

**COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES****Field of the Invention**

5           The present invention relates to compositions and methods useful for the diagnosis and treatment of immune related diseases.

**Background of the Invention**

10           Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

15           Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

20           Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

25           T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, *etc.* The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, *i.e.*, lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate  
30 in the immune response.

35           Immune related diseases could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

40           CD4+ T cells are known to be important regulators of inflammation. Herein, CD4+ T cells were activated and the profile of genes differentially expressed upon activation was analyzed. As such, the activation specific genes may be potential therapeutic targets. *In vivo* co-stimulation is necessary for a productive immune proliferative response. The list of costimulatory molecules is quite extensive and it is still unclear just which co-stimulatory molecules play critical roles in different types and stages of

inflammation. In this application the focus is on genes which are specifically upregulated or downregulated by stimulation with anti-CD3/ICAM, or anti-CD3/anti-CD28 and may be useful in targeting inflammatory processes which are associated with these different molecules.

Despite the above identified advances in T cell research, there is a great need for additional diagnostic and therapeutic agents capable of detecting the presence of a T cell mediated disorders in a mammal and for effectively reducing these disorders. Accordingly, it is an objective of the present invention to identify polypeptides that are overexpressed in activated T cells as compared to resting T cells, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of T cell mediated disorders in mammals.

### Summary of the Invention

#### A. Embodiments

The present invention concerns compositions and methods useful for the diagnosis and treatment of immune related disease in mammals, including humans. The present invention is based on the identification of proteins (including agonist and antagonist antibodies) which are a result of stimulation of the immune response in mammals. Immune related diseases can be treated by suppressing or enhancing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial. Alternatively, molecules that suppress the immune response attenuate or reduce the immune response to an antigen (*e.g.*, neutralizing antibodies) can be used therapeutically where attenuation of the immune response would be beneficial (*e.g.*, inflammation). Accordingly, the PRO polypeptides, agonists and antagonists thereof are also useful to prepare medicines and medicaments for the treatment of immune-related and inflammatory diseases. In a specific aspect, such medicines and medicaments comprise a therapeutically effective amount of a PRO polypeptide, agonist or antagonist thereof with a pharmaceutically acceptable carrier. Preferably, the admixture is sterile.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprises contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native sequence PRO polypeptide. In a specific aspect, the PRO agonist or antagonist is an anti-PRO antibody.

In another embodiment, the invention concerns a composition of matter comprising a PRO polypeptide or an agonist or antagonist antibody which binds the polypeptide in admixture with a carrier or excipient. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide or antibody. In another aspect, when the composition comprises an immune stimulating molecule, the composition is useful for: (a) increasing infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) stimulating or enhancing an immune response in a mammal in need thereof, (c) increasing the proliferation of T-lymphocytes in a mammal in need thereof in response to an antigen, (d) stimulating the activity of T-lymphocytes or (e) increasing the vascular permeability. In a further aspect, when the composition comprises an immune inhibiting molecule, the composition is useful for: (a) decreasing infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) inhibiting or reducing an

immune response in a mammal in need thereof, (c) decreasing the activity of T-lymphocytes or (d) decreasing the proliferation of T-lymphocytes in a mammal in need thereof in response to an antigen. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

5 In another embodiment, the invention concerns a method of treating an immune related disorder in a mammal in need thereof, comprising administering to the mammal an effective amount of a PRO polypeptide, an agonist thereof, or an antagonist thereto. In a preferred aspect, the immune related disorder is selected from the group consisting of: systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, demyelinating diseases of 10 the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious, autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation 15 associated diseases including graft rejection and graft -versus-host-disease.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody. In one aspect, the present invention concerns an isolated antibody which binds a PRO polypeptide. In another aspect, the antibody mimics the activity of a 25 PRO polypeptide (an agonist antibody) or conversely the antibody inhibits or neutralizes the activity of a PRO polypeptide (an antagonist antibody). In another aspect, the antibody is a monoclonal antibody, which preferably has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a monoclonal antibody, a single-chain antibody, or an anti-idiotypic 30 antibody.

In yet another embodiment, the present invention provides a composition comprising an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the antibody. Preferably, the composition is sterile. The composition may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve 35 extended storage stability. Alternatively, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

In a further embodiment, the invention concerns an article of manufacture, comprising:

- (a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;
- (b) a container containing said composition; and

(c) a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of an immune related disease. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

5 In yet another embodiment, the present invention concerns a method of diagnosing an immune related disease in a mammal, comprising detecting the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample indicates the presence of immune related disease in the mammal  
10 from which the test tissue cells were obtained.

In another embodiment, the present invention concerns a method of diagnosing an immune disease in a mammal, comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and a PRO polypeptide, in the test sample; wherein the formation of said complex is indicative of the presence or  
15 absence of said disease. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence or absence of an immune disease in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light  
20 microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected of having a deficiency or abnormality of the immune system.

In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a test sample of cells suspected of containing the PRO polypeptide to an anti-PRO antibody and determining the binding of said antibody to said cell sample. In a  
25 specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

In another embodiment, the present invention concerns an immune-related disease diagnostic kit, comprising an anti-PRO antibody and a carrier in suitable packaging. The kit preferably contains instructions for using the antibody to detect the presence of the PRO polypeptide. Preferably the carrier is  
30 pharmaceutically acceptable.

In another embodiment, the present invention concerns a diagnostic kit, containing an anti-PRO antibody in suitable packaging. The kit preferably contains instructions for using the antibody to detect the PRO polypeptide.

In another embodiment, the invention provides a method of diagnosing an immune-related disease  
35 in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of the PRO polypeptide in said test sample is indicative of the presence of an immune-related disease in said mammal.

In another embodiment, the present invention concerns a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the invention concerns a method for identifying a compound capable of inhibiting the activity of a PRO polypeptide comprising contacting a candidate compound with a PRO polypeptide under conditions and for a time sufficient to allow these two components to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific aspect, either the candidate compound or the PRO polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally express the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

In yet another embodiment, the present invention concerns a method for treating an immune-related disorder in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the nucleic acid is administered via *ex vivo* gene therapy. In a further preferred embodiment, the nucleic acid is comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral or retroviral vector.

In yet another aspect, the invention provides a recombinant viral particle comprising a viral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the viral vector is in association with viral structural proteins. Preferably, the signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention concerns an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce recombinant retroviral particles.

In a still further embodiment, the invention provides a method of increasing the activity of T-lymphocytes in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the activity of T-lymphocytes in the mammal is increased.

5 In a still further embodiment, the invention provides a method of decreasing the activity of T-lymphocytes in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the activity of T-lymphocytes in the mammal is decreased.

10 In a still further embodiment, the invention provides a method of increasing the proliferation of T-lymphocytes in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the proliferation of T-lymphocytes in the mammal is increased.

15 In a still further embodiment, the invention provides a method of decreasing the proliferation of T-lymphocytes in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the proliferation of T-lymphocytes in the mammal is decreased.

B. Additional Embodiments

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided.  
20 By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

25 In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

30 In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

35 In other embodiments, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity,  
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alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid

sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700 nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences herein above identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as herein before described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the

appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as herein before described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

## List of Figures

- Figure 1: DNA325395, NP\_000973.2, 200012\_x.at  
 Figure 2: PRO81927  
 Figure 3: DNA329897, NP\_031401.1, 200020.at  
 Figure 4: PRO69676  
 Figure 5: DNA326769, NP\_001000.2, 200024.at  
 Figure 6: PRO83105  
 Figure 7: DNA329898, NP\_000979.1, 200025\_s.at  
 Figure 8: PRO10643  
 Figure 9: DNA293451, NP\_296374.1, 200026.at  
 Figure 10: PRO70720  
 Figure 11: DNA326466, NP\_004530.1, 200027.at  
 Figure 12: PRO60800  
 Figure 13: DNA329899, NP\_002785.1, 200039\_s.at  
 Figure 14: PRO69614  
 Figure 15: DNA326953, HSPC117, 200042.at  
 Figure 16: PRO83270  
 Figure 17: DNA255084, NP\_001081.1, 200045.at  
 Figure 18: PRO50170  
 Figure 19: DNA272614, NP\_004506.1, 200052\_s.at  
 Figure 20: PRO60747  
 Figure 21: DNA304680, HSPCB, 200064.at  
 Figure 22: PRO71106  
 Figure 23: DNA189703, NP\_005539.1, 200079\_s.at  
 Figure 24: PRO22637  
 Figure 25: DNA329900, NP\_002905.1, 1053.at  
 Figure 26: PRO81549  
 Figure 27: DNA88189, NP\_037362.1, 266\_s.at  
 Figure 28: PRO2690  
 Figure 29: DNA272992, NP\_055479.1, 32069.at  
 Figure 30: PRO61064  
 Figure 31A-B: DNA329901, BAA32291.2, 32091.at  
 Figure 32: PRO85218  
 Figure 33: DNA329902, NP\_110419.2, 32502.at  
 Figure 34: PRO85219  
 Figure 35: DNA329903, NP\_005596.2, 32541.at  
 Figure 36: PRO85220  
 Figure 37: DNA327521, NP\_002192.2, 33304.at  
 Figure 38: PRO58320  
 Figure 39: DNA272223, NP\_004444.1, 33494.at  
 Figure 40: PRO60485  
 Figure 41A-B: DNA329904, NP\_066554.1, 33767.at  
 Figure 42: PRO85221  
 Figure 43: DNA210121, NP\_001794.1, 34210.at  
 Figure 44: PRO33667  
 Figure 45: DNA269828, NP\_006691.1, 35254.at  
 Figure 46: PRO58230  
 Figure 47: DNA88643, NP\_000190.1, 35626.at  
 Figure 48: PRO2455  
 Figure 49: DNA331435, NP\_006143.1, 35974.at  
 Figure 50: PRO86495  
 Figure 51A-B: DNA272022, NP\_002607.1, 36829.at  
 Figure 52: PRO60296  
 Figure 53: DNA226967, NP\_055145.2, 37028.at  
 Figure 54: PRO37430  
 Figure 55: DNA226043, NP\_006424.2, 37145.at  
 Figure 56: PRO36506  
 Figure 57: DNA329906, MGC14258, 37577.at  
 Figure 58: PRO85223  
 Figure 59: DNA256295, NP\_002310.1, 37796.at  
 Figure 60: PRO51339  
 Figure 61: DNA328354, AF237769, 37966.at  
 Figure 62: PRO84215  
 Figure 63A-B: DNA329907, NP\_036423.1, 38158.at  
 Figure 64: PRO85224  
 Figure 65A-B: DNA329908, BAA13246.1, 38892.at  
 Figure 66: PRO85225  
 Figure 67: DNA328356, BC013566, 39248.at  
 Figure 68: PRO38028  
 Figure 69: DNA327523, NP\_004916.1, 39249.at  
 Figure 70: PRO38028  
 Figure 71A-B: DNA328358, STK10, 40420.at  
 Figure 72: PRO84218  
 Figure 73: DNA329909, NP\_077084.1, 40446.at  
 Figure 74: PRO62251  
 Figure 75: DNA329910, NP\_003251.2, 40837.at  
 Figure 76: PRO82891  
 Figure 77A-B: DNA329093, NP\_006631.1, 41220.at  
 Figure 78: PRO84745  
 Figure 79A-C: DNA331436, 7689629.6, 43427.at  
 Figure 80: PRO86496  
 Figure 81: DNA154653, DNA154653, 43511\_s.at  
 Figure 82: DNA262129, NP\_079389.1, 44790\_s.at  
 Figure 83: PRO54740  
 Figure 84: DNA326185, NP\_073607.2, 45633.at  
 Figure 85: PRO82602  
 Figure 86: DNA329912, NP\_004614.1, 46167.at  
 Figure 87: PRO85227  
 Figure 88: DNA329913, SSB-3, 46256.at  
 Figure 89: PRO85228  
 Figure 90: DNA324145, NP\_060259.1, 46665.at  
 Figure 91: PRO80846  
 Figure 92: DNA329094, NP\_077285.1, 48531.at  
 Figure 93: PRO84746  
 Figure 94: DNA329914, NP\_079175.2, 52285\_f.at  
 Figure 95: PRO85229  
 Figure 96: DNA328364, NP\_068577.1, 52940.at  
 Figure 97: PRO84223  
 Figure 98: DNA329915, NP\_065093.1, 56197.at  
 Figure 99: PRO85230  
 Figure 100A-B: DNA328966, AK024397, 57082.at  
 Figure 101: PRO84670  
 Figure 102A-B: DNA226870, NP\_000782.1, 48808.at  
 Figure 103: PRO37333  
 Figure 104: DNA328366, NP\_079233.1, 59375.at  
 Figure 105: PRO84225  
 Figure 106: DNA331437, 338326.15, 60084.at  
 Figure 107: PRO86497  
 Figure 108: DNA328367, NP\_079108.2, 60471.at

- Figure 109: PRO84226  
Figure 110: DNA327876, NP\_005081.1, 60528.at  
Figure 111: PRO83815  
Figure 112: DNA329917, NP\_065174.1, 64486.at  
Figure 113: PRO85232  
Figure 114: DNA329918, BC008671, 65630.at  
Figure 115: PRO85233  
Figure 116A-B: DNA196428, BAA31649.1, 76897.s.at  
Figure 117: PRO71274  
Figure 118: DNA329919, C20orf67, 89948.at  
Figure 119: PRO85234  
Figure 120: DNA328369, BC007634, 90610.at  
Figure 121: DNA269410, NP\_002725.1, 200605.s.at  
Figure 122: PRO57836  
Figure 123A-B: DNA326380, NP\_004850.1, 200614.at  
Figure 124: PRO82774  
Figure 125A-B: DNA194778, NP\_055545.1, 200616.s.at  
Figure 126: PRO24056  
Figure 127: DNA287245, NP\_004175.1, 200628.s.at  
Figure 128: PRO69520  
Figure 129: DNA287245, WARS, 200629.at  
Figure 130: PRO69520  
Figure 131: DNA327532, GLUL, 200648.s.at  
Figure 132: PRO71134  
Figure 133: DNA97285, NP\_005557.1, 200650.s.at  
Figure 134: PRO3632  
Figure 135: DNA226125, NP\_003136.1, 200652.at  
Figure 136: PRO36588  
Figure 137: DNA325923, NP\_008819.1, 200655.s.at  
Figure 138: PRO4904  
Figure 139: DNA227055, NP\_002625.1, 200658.s.at  
Figure 140: PRO37518  
Figure 141: DNA275062, NP\_006136.1, 200664.s.at  
Figure 142: PRO62782  
Figure 143: DNA275062, DNAJB1, 200666.s.at  
Figure 144: PRO62782  
Figure 145A-B: DNA328372, 105551.7, 200685.at  
Figure 146: PRO84229  
Figure 147A-B: DNA329920, NP\_036558.1, 200687.s.at  
Figure 148: PRO85235  
Figure 149: DNA324633, BC000478, 200691.s.at  
Figure 150: PRO81277  
Figure 151: DNA324897, NP\_006845.1, 200700.s.at  
Figure 152: PRO12468  
Figure 153: DNA275267, NP\_003737.1, 200703.at  
Figure 154: PRO62952  
Figure 155: DNA328373, AB034747, 200704.at  
Figure 156: PRO84230  
Figure 157: DNA328374, NP\_004853.1, 200706.s.at  
Figure 158: PRO84231  
Figure 159: DNA290260, NP\_036555.1, 200715.x.at  
Figure 160: PRO70385  
Figure 161: DNA329921, 1315403.9, 200719.at  
Figure 162: PRO85236  
Figure 163: DNA329538, M11S1, 200722.s.at  
Figure 164: PRO85088  
Figure 165: DNA227618, HSGPIP137, 200723.s.at  
Figure 166: PRO38081  
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Figure 168: PRO62466  
Figure 169A-B: DNA327534, NP\_003454.1, 200730.s.at  
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Figure 171A-B: DNA327534, PTP4A1, 200731.s.at  
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Figure 173: DNA331438, 402431.7, 200732.s.at  
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Figure 177: DNA327845, PGK1, 200738.s.at  
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Figure 179: DNA287207, NP\_006316.1, 200750.s.at  
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Figure 181A-B: DNA274977, HSU97105, 200762.at  
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Figure 185: DNA324135, NP\_005902.1, 200769.s.at  
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Figure 201: DNA287211, HSPD1, 200807.s.at  
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Figure 205: DNA269874, CIRBP, 200811.at  
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Figure 208: PRO38258  
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Figure 213A-B: DNA328378, AB032261, 200832.s.at  
Figure 214: PRO84233  
Figure 215: DNA329922, CTSB, 200838.at  
Figure 216: PRO3344

- Figure 217: DNA88165, HUMCTSB, 200839.s.at  
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 Figure 223A-C: DNA331439, NP\_001447.1, 200859.x.at  
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 Figure 225A-B: DNA228029, NP\_055577.1, 200862.at  
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 Figure 229: DNA226112, PSAP, 200871.s.at  
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 Figure 235: DNA324107, NP\_006421.1, 200877.at  
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 Figure 253: DNA328380, HSHLAEHCM, 200904.at  
 Figure 254: DNA304665, NP\_000995.1, 200909.s.at  
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 Figure 258: DNA272695, BTG1, 200921.s.at  
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 Figure 260: DNA227077, NP\_005558.1, 200923.at  
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 Figure 262: DNA327255, NP\_002385.2, 200924.s.at  
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 Figure 265: PRO36341  
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 Figure 267: PRO85239  
 Figure 268A-B: DNA287217, NP\_001750.1, 200951.s.at  
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 Figure 270A-B: DNA287217, CCND2, 200952.s.at  
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 Figure 276A-B: DNA331289, ABLIM1, 200965.s.at  
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 Figure 278: DNA287355, NP\_000025.1, 200966.x.at  
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 Figure 284A-B: DNA325896, NP\_001521.1, 200989.at  
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 Figure 295: DNA304713, TXNIP, 201009.s.at  
 Figure 296: PRO71139  
 Figure 297: DNA304713, S73591, 201010.s.at  
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 Figure 300: PRO2907  
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 Figure 303: DNA328388, NP\_006443.1, 201014.s.at  
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 Figure 306: PRO11993  
 Figure 307A-B: DNA329101, NP\_056988.2, 201024.x.at  
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 Figure 309A-B: DNA329101, IF2, 201027.s.at  
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 Figure 319: DNA254725, NP\_002257.1, 201088.at  
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 Figure 321: DNA329930, ATP6V1B2, 201089.at  
 Figure 322: PRO85243  
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 Figure 324: PRO69484

- Figure 325A-B: DNA328395, NP\_056198.1, 201104.x.at  
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Figure 327: DNA304719, NP\_002296.1, 201105.at  
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Figure 335: PRO82678  
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Figure 342: DNA329105, NP\_006109.2, 201145.at  
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Figure 349: PRO12890  
Figure 350: DNA151802, BHLHB2, 201170.s.at  
Figure 351: PRO12890  
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Figure 353: PRO61345  
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Figure 355: PRO86501  
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Figure 372A-B: DNA328404, NP\_003321.1, 201266.at  
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Figure 382A-B: DNA327545, TOP2A, 201291.s.at  
Figure 383: PRO82731  
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Figure 387A-B: DNA226778, HSM800772, 201295.s.at  
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Figure 405: DNA329002, NP\_001753.1, 201327.s.at  
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Figure 417A-B: DNA329108, 1383643.16, 201368.at  
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- Figure 434: PRO84257  
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 Figure 437: DNA329939, 1393503.1, 201417.at  
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 Figure 443: DNA272286, NP\_001743.1, 201432.at  
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 Figure 447A-C: DNA88140, COL6A3, 201438.at  
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 Figure 457: DNA226359, JUN, 201465.s.at  
 Figure 458: PRO36822  
 Figure 459: DNA226359, DNA226359, 201466.s.at  
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 Figure 462: PRO84258  
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 Figure 469: DNA327551, RRM1, 201477.s.at  
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 Figure 477: DNA304459, NP\_005720.1, 201490.s.at  
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 Figure 485: DNA323741, NP\_003123.1, 201516.at  
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 Figure 490: PRO84261  
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 Figure 493: DNA329943, NP\_009037.1, 201534.s.at  
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 Figure 495: DNA331448, UBL3, 201535.at  
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 Figure 498: PRO60438  
 Figure 499: DNA226291, NP\_055047.1, 201556.s.at  
 Figure 500: PRO36754  
 Figure 501: DNA226291, VAMP2, 201557.at  
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 Figure 507: DNA327199, NP\_066979.1, 201580.s.at  
 Figure 508: PRO83475  
 Figure 509A-B: DNA329944, AB032988, 201581.at  
 Figure 510: DNA329945, NP\_006354.2, 201583.s.at  
 Figure 511: PRO85252  
 Figure 512A-B: DNA329946, D80000, 201589.at  
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 Figure 514: PRO70425  
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 Figure 516: PRO37674  
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 Figure 518: PRO60991  
 Figure 519: DNA255406, NP\_005533.1, 201625.s.at  
 Figure 520: PRO50473  
 Figure 521: DNA255406, INSIG1, 201627.s.at  
 Figure 522: PRO50473  
 Figure 523: DNA329115, NP\_434702.1, 201631.s.at  
 Figure 524: PRO84760  
 Figure 525: DNA287240, NP\_004326.1, 201641.at  
 Figure 526: PRO29371  
 Figure 527: DNA327557, NP\_004214.1, 201649.at  
 Figure 528: PRO83588  
 Figure 529A-B: DNA220748, NP\_000201.1, 201656.at  
 Figure 530: PRO34726  
 Figure 531A-B: DNA328422, NP\_004448.1, 201662.s.at  
 Figure 532: PRO84263  
 Figure 533A-B: DNA273732, NP\_005487.2, 201663.s.at  
 Figure 534: PRO61695  
 Figure 535A-B: DNA273732, HSM801845, 201664.at  
 Figure 536: PRO61695  
 Figure 537: DNA273090, NP\_002347.4, 201669.s.at  
 Figure 538: PRO61148  
 Figure 539: DNA273090, MARCKS, 201670.s.at  
 Figure 540: PRO61148  
 Figure 541: DNA290244, NP\_000261.1, 201695.s.at  
 Figure 542: PRO70353  
 Figure 543: DNA329948, NP\_002797.1, 201699.at

- Figure 544: PRO85253  
 Figure 545: DNA324742, NP\_001751.1, 201700\_at  
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 Figure 547: DNA270883, NP\_001061.1, 201714\_at  
 Figure 548: PRO59218  
 Figure 549A-B: DNA151806, NP\_001422.1, 201719\_s.at  
 Figure 550: PRO12768  
 Figure 551: DNA227461, NP\_006753.1, 201720\_s.at  
 Figure 552: PRO37924  
 Figure 553: DNA227461, LAPT5, 201721\_s.at  
 Figure 554: PRO37924  
 Figure 555: DNA329949, BC003376, 201726\_at  
 Figure 556: PRO85254  
 Figure 557: DNA227576, NP\_005618.1, 201739\_at  
 Figure 558: PRO38039  
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 Figure 560: PRO82769  
 Figure 561: DNA327559, NP\_058432.1, 201752\_s.at  
 Figure 562: PRO83589  
 Figure 563: DNA331294, ADD3, 201753\_s.at  
 Figure 564: PRO86393  
 Figure 565: DNA227035, NP\_006730.1, 201755\_at  
 Figure 566: PRO37498  
 Figure 567: DNA329016, NP\_006283.1, 201758\_at  
 Figure 568: PRO4887  
 Figure 569: DNA328427, NP\_061109.1, 201760\_s.at  
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 Figure 571: DNA287167, NP\_006627.1, 201761\_at  
 Figure 572: PRO59136  
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 Figure 574: PRO69491  
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 Figure 576: PRO11558  
 Figure 577A-B: DNA329951, NP\_055680.1, 201774\_s.at  
 Figure 578: PRO85255  
 Figure 579: DNA151017, NP\_004835.1, 201810\_s.at  
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 Figure 581: DNA151017, SH3BP5, 201811\_x.at  
 Figure 582: PRO12841  
 Figure 583: DNA227929, NP\_061932.1, 201812\_s.at  
 Figure 584: PRO38392  
 Figure 585: DNA324015, NP\_006326.1, 201821\_s.at  
 Figure 586: PRO80735  
 Figure 587: DNA329952, BC010285, 201829\_at  
 Figure 588: PRO85256  
 Figure 589: DNA329952, NET1, 201830\_s.at  
 Figure 590: PRO85256  
 Figure 591: DNA329954, NP\_001518.1, 201833\_at  
 Figure 592: PRO85258  
 Figure 593A-B: DNA329955, AB029551, 201845\_s.at  
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 Figure 595: DNA254350, NP\_004043.2, 201848\_s.at  
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 Figure 597: DNA254350, BNIP3, 201849\_at  
 Figure 598: PRO49461  
 Figure 599: DNA329118, NP\_068660.1, 201853\_s.at  
 Figure 600: PRO83123  
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 Figure 602: PRO60337  
 Figure 603: DNA150805, NP\_055703.1, 201889\_at  
 Figure 604: PRO11583  
 Figure 605: DNA253582, DNA253582, 201890\_at  
 Figure 606: PRO49181  
 Figure 607: DNA329956, NP\_000875.1, 201892\_s.at  
 Figure 608: PRO85260  
 Figure 609: DNA328431, NP\_001817.1, 201897\_s.at  
 Figure 610: PRO45093  
 Figure 611: DNA254978, NP\_060625.1, 201917\_s.at  
 Figure 612: PRO50067  
 Figure 613: DNA329057, NP\_004116.2, 201921\_at  
 Figure 614: PRO84719  
 Figure 615: DNA227112, NP\_006397.1, 201923\_at  
 Figure 616: PRO37575  
 Figure 617: DNA275240, NP\_005906.2, 201930\_at  
 Figure 618: PRO62927  
 Figure 619: DNA273014, NP\_000117.1, 201931\_at  
 Figure 620: PRO61085  
 Figure 621A-B: DNA329120, NP\_002560.1, 201945\_at  
 Figure 622: PRO2752  
 Figure 623: DNA274167, NP\_006422.1, 201946\_s.at  
 Figure 624: PRO62097  
 Figure 625: DNA274167, CCT2, 201947\_s.at  
 Figure 626: PRO62097  
 Figure 627: DNA103481, NP\_037417.1, 201948\_at  
 Figure 628: PRO4808  
 Figure 629A-B: DNA327563, NP\_066945.1, 201963\_at  
 Figure 630: PRO83592  
 Figure 631: DNA275214, NP\_002473.1, 201970\_s.at  
 Figure 632: PRO62908  
 Figure 633A-B: DNA328433, ATP6V1A1, 201971\_s.at  
 Figure 634: PRO84268  
 Figure 635A-B: DNA272191, NP\_002947.1, 201975\_at  
 Figure 636: PRO60456  
 Figure 637: DNA328809, PTPN12, 202006\_at  
 Figure 638: PRO4803  
 Figure 639: DNA328437, AF083441, 202021\_x.at  
 Figure 640: PRO84271  
 Figure 641: DNA329957, NP\_005156.1, 202022\_at  
 Figure 642: PRO85261  
 Figure 643A-B: DNA329958, NP\_510880.1, 202039\_at  
 Figure 644: PRO85262  
 Figure 645: DNA327017, NP\_004586.2, 202043\_s.at  
 Figure 646: PRO61744  
 Figure 647A-B: DNA227985, NP\_055107.1, 202047\_s.at  
 Figure 648: PRO38448  
 Figure 649A-B: DNA225991, NP\_000518.1, 202067\_s.at  
 Figure 650: PRO36454

Figure 651A-B: DNA225991, LDLR, 202068.s.at  
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 Figure 653: DNA327567, NP\_005521.1, 202069.s.at  
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 Figure 659: DNA327568, NP\_002453.1, 202086.at  
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 Figure 661: DNA327569, CTSL, 202087.s.at  
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 Figure 663: DNA329959, 251651.5, 202094.at  
 Figure 664: PRO85263  
 Figure 665: DNA129504, NP\_001159.1, 202095.s.at  
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 Figure 668: PRO84274  
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 Figure 711: DNA150808, GBP1, 202270.at  
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 Figure 715: DNA304716, NP\_510867.1, 202284.s.at  
 Figure 716: PRO71142  
 Figure 717: DNA331450, NP\_004381.1, 202295.s.at  
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 Figure 723A-B: DNA151108, NP\_004167.3, 202308.at  
 Figure 724: PRO12105  
 Figure 725: DNA270142, NP\_005947.2, 202309.at  
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 Figure 731: DNA331451, UNG, 202330.s.at  
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 Figure 733A-B: DNA329970, NP\_000910.2, 202336.s.at  
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 Figure 735: DNA255088, NP\_003249.1, 202338.at  
 Figure 736: PRO50174  
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 Figure 739: DNA270502, NP\_002807.1, 202352.s.at  
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 Figure 754: PRO12304  
 Figure 755: DNA88332, NP\_002026.1, 202419.at  
 Figure 756: PRO2753  
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 Figure 762: PRO1213  
 Figure 763: DNA103322, NP\_005818.1, 202433.at  
 Figure 764: PRO4652  
 Figure 765: DNA68868, DNA68868, 202441.at  
 Figure 766: PRO1460  
 Figure 767: DNA227121, PLSCR1, 202446.s.at  
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 Figure 770: PRO85274  
 Figure 771A-B: DNA329973, NP\_055461.1, 202459.s.at  
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 Figure 773A-B: DNA269642, NP\_004557.1, 202464.s.at  
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 Figure 775: DNA227921, NP\_003789.1, 202468.s.at  
 Figure 776: PRO38384  
 Figure 777A-B: DNA329122, NP\_067675.1, 202478.at  
 Figure 778: PRO84764  
 Figure 779: DNA329123, NP\_002873.1, 202483.s.at  
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 Figure 783: DNA329974, NP\_055083.1, 202501.at  
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 Figure 787A-B: DNA273879, NP\_055753.1, 202519.at  
 Figure 788: PRO61835  
 Figure 789A-B: DNA277809, NP\_055582.1, 202524.s.at  
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 Figure 791: DNA328452, NP\_000394.1, 202528.at  
 Figure 792: PRO63289  
 Figure 793A-B: DNA226870, DHFR, 202532.s.at  
 Figure 794: PRO37333  
 Figure 795: DNA331452, BC003584, 202533.s.at  
 Figure 796: PRO86506  
 Figure 797: DNA331453, NP\_060993.1, 202534.x.at  
 Figure 798: PRO69586  
 Figure 799: DNA329976, NP\_003815.1, 202535.at  
 Figure 800: PRO4801  
 Figure 801: DNA329977, BC001553, 202536.at  
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 Figure 803A-B: DNA255105, NP\_000850.1, 202539.s.at  
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 Figure 805A-B: DNA255105, HMGCR, 202540.s.at  
 Figure 806: PRO50187  
 Figure 807A-B: DNA274852, NP\_004115.1, 202543.s.at  
 Figure 808: PRO62605  
 Figure 809: DNA275244, DNA275244, 202557.at  
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 Figure 812A-C: DNA329978, SVIL, 202566.s.at  
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 Figure 815: PRO83257  
 Figure 816: DNA325587, NP\_068772.1, 202580.x.at  
 Figure 817: PRO82083  
 Figure 818: DNA227607, HSPA1B, 202581.at  
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 Figure 821: PRO84283  
 Figure 822: DNA329979, NP\_001062.1, 202589.at  
 Figure 823: PRO82821  
 Figure 824: DNA329125, NP\_056159.1, 202595.s.at  
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 Figure 828A-C: DNA270287, NRIP1, 202600.s.at  
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 Figure 837: PRO84768  
 Figure 838: DNA59763, NP\_000192.1, 202637.s.at  
 Figure 839: PRO160  
 Figure 840: DNA59763, ICAM1, 202638.s.at  
 Figure 841: PRO160  
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 Figure 846A-B: DNA151841, TNFAIP3, 202644.s.at  
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 Figure 848: DNA329981, NP\_001155.1, 202652.at  
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 Figure 855: PRO69681  
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 Figure 857: PRO69486  
 Figure 858: DNA289526, ATF3, 202672.s.at

- Figure 859: PRO70282  
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Figure 861: PRO1096  
Figure 862: DNA84130, TNFSF10, 202688.at  
Figure 863: PRO1096  
Figure 864: DNA329982, NP\_008937.1, 202697.at  
Figure 865: PRO85279  
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Figure 870: DNA326000, NP\_004692.1, 202705.at  
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Figure 872: DNA273371, NP\_000364.1, 202706.s.at  
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Figure 876: DNA43010, NP\_000588.1, 202718.at  
Figure 877: PRO36145  
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Figure 879: PRO58642  
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Figure 881: PRO12082  
Figure 882: DNA58828, DNA58828, 202746.at  
Figure 883: PRO1189  
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Figure 886: DNA227133, NP\_004111.1, 202748.at  
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Figure 892: DNA329008, NP\_004337.2, 202763.at  
Figure 893: PRO12832  
Figure 894A-B: DNA328464, 977954.20, 202769.at  
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Figure 898: DNA273346, NP\_055316.1, 202779.s.at  
Figure 899: PRO61349  
Figure 900: DNA329985, NP\_002185.1, 202794.at  
Figure 901: PRO60589  
Figure 902: DNA88428, NP\_000202.1, 202803.s.at  
Figure 903: PRO2787  
Figure 904: DNA329986, NP\_006454.1, 202811.at  
Figure 905: PRO61895  
Figure 906A-B: DNA226364, NP\_001612.1, 202820.at  
Figure 907: PRO36827  
Figure 908: DNA328465, NP\_005639.1, 202823.at  
Figure 909: PRO84291  
Figure 910: DNA329987, NP\_000286.2, 202833.s.at  
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Figure 912: DNA269828, FLN29, 202837.at  
Figure 913: PRO58230  
Figure 914: DNA329988, NP\_036460.1, 202842.s.at  
Figure 915: PRO1471  
Figure 916: DNA329988, DNAJB9, 202843.at  
Figure 917: PRO1471  
Figure 918: DNA103394, NP\_004198.1, 202855.s.at  
Figure 919: PRO4722  
Figure 920: DNA103394, SLC16A3, 202856.s.at  
Figure 921: PRO4722  
Figure 922A-B: DNA272022, PER1, 202861.at  
Figure 923: PRO60296  
Figure 924: DNA275144, NP\_000128.1, 202862.at  
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Figure 926: DNA328467, SP100, 202864.s.at  
Figure 927: PRO84293  
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Figure 929: PRO69559  
Figure 930: DNA273060, NP\_001246.1, 202870.s.at  
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Figure 932: DNA329130, NP\_004286.2, 202871.at  
Figure 933: PRO20124  
Figure 934: DNA328469, NP\_001686.1, 202874.s.at  
Figure 935: PRO84295  
Figure 936: DNA271881, PSCD1, 202880.s.at  
Figure 937: PRO60160  
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Figure 941A-B: DNA225538, NBS1, 202907.s.at  
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Figure 944: PRO84309  
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Figure 955: DNA328471, ZMPSTE24, 202939.at  
Figure 956: PRO84297  
Figure 957: DNA304681, NP\_066552.1, 202941.at  
Figure 958: PRO71107  
Figure 959: DNA269481, NP\_001976.1, 202942.at  
Figure 960: PRO57901  
Figure 961: DNA273320, NP\_008950.1, 202954.at  
Figure 962: PRO61327  
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Figure 964: PRO61341  
Figure 965A-B: DNA328473, NP\_006473.1,

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Figure 967A-B: DNA227293, NP\_055698.1, 202972.s\_at  
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Figure 969A-B: DNA227293, KIAA0914, 202973.x\_at  
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Figure 972: PRO58102  
Figure 973: DNA274034, NP\_006388.1, 203022.at  
Figure 974: PRO61977  
Figure 975: DNA329136, NP\_057475.1, 203023.at  
Figure 976: PRO84772  
Figure 977A-B: DNA271865, NP\_055566.1, 203037.s\_at  
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Figure 979A-B: DNA304464, NP\_055733.1, 203044.at  
Figure 980: PRO71042  
Figure 981A-B: DNA329991, NP\_003911.1, 203046.s\_at  
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Figure 983: DNA331457, AF119894, 203047.at  
Figure 984: PRO86509  
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Figure 986: PRO12565  
Figure 987: DNA326693, NP\_004697.2, 203055.s\_at  
Figure 988: PRO83039  
Figure 989: DNA188357, NP\_000651.1, 203085.s\_at  
Figure 990: PRO21897  
Figure 991: DNA324133, NP\_037379.1, 203089.s\_at  
Figure 992: PRO80835  
Figure 993: DNA269984, NP\_055443.1, 203094.at  
Figure 994: PRO58380  
Figure 995: DNA329992, NP\_002399.1, 203102.s\_at  
Figure 996: PRO59267  
Figure 997: DNA329993, NP\_115754.1, 203113.s\_at  
Figure 998: PRO85285  
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Figure 1000: PRO85286  
Figure 1001A-B: DNA150447, NP\_004854.1, 203128.at  
Figure 1002: PRO12256  
Figure 1003: DNA254543, NP\_006799.1, 203133.at  
Figure 1004: PRO49648  
Figure 1005: DNA269918, NP\_003633.1, 203138.at  
Figure 1006: PRO58316  
Figure 1007: DNA329001, BCL6, 203140.at  
Figure 1008: PRO26296  
Figure 1009A-B: DNA329995, NP\_006452.1, 203145.at  
Figure 1010: PRO85287  
Figure 1011A-B: DNA226330, NP\_001461.1, 203146.s\_at  
Figure 1012: PRO36793  
Figure 1013: DNA271624, NP\_001539.1, 203153.at  
Figure 1014: PRO59911  
Figure 1015: DNA269660, NP\_003192.1, 203177.x\_at  
Figure 1016: PRO58071  
Figure 1017: DNA304720, NP\_062427.1, 203186.s\_at  
Figure 1018: PRO71146  
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Figure 1022: PRO61115  
Figure 1023: DNA329997, NP\_031396.1, 203210.s\_at  
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Figure 1025A-B: DNA328481, MTMR2, 203211.s\_at  
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Figure 1028: PRO86510  
Figure 1029: DNA331459, CDC2, 203214.x\_at  
Figure 1030: PRO70806  
Figure 1031: DNA76514, NP\_000409.1, 203233.at  
Figure 1032: PRO2540  
Figure 1033: DNA325507, NP\_005842.1, 203252.at  
Figure 1034: PRO69461  
Figure 1035: DNA330000, NP\_036277.1, 203270.at  
Figure 1036: PRO85289  
Figure 1037: DNA302020, NP\_005564.1, 203276.at  
Figure 1038: PRO70993  
Figure 1039: DNA328486, NP\_000149.1, 203282.at  
Figure 1040: PRO60119  
Figure 1041A-B: DNA330001, NP\_036394.1, 203285.s\_at  
Figure 1042: PRO85290  
Figure 1043: DNA225675, NP\_005561.1, 203293.s\_at  
Figure 1044: PRO36138  
Figure 1045: DNA330002, BC007195, 203315.at  
Figure 1046: PRO80853  
Figure 1047A-B: DNA330003, NP\_005532.1, 203331.s\_at  
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Figure 1049: DNA330004, NP\_055785.2, 203333.at  
Figure 1050: PRO85292  
Figure 1051: DNA330005, NP\_003696.2, 203340.s\_at  
Figure 1052: PRO85293  
Figure 1053: DNA271959, NP\_002885.1, 203344.s\_at  
Figure 1054: PRO60234  
Figure 1055: DNA330006, NP\_031384.1, 203347.s\_at  
Figure 1056: PRO85294  
Figure 1057: DNA330007, NP\_055111.1, 203357.s\_at  
Figure 1058: PRO85295  
Figure 1059: DNA330008, NP\_004447.2, 203358.s\_at  
Figure 1060: PRO85296  
Figure 1061: DNA272449, NP\_036465.1, 203360.s\_at  
Figure 1062: PRO60698  
Figure 1063: DNA324514, NP\_002349.1, 203362.s\_at  
Figure 1064: PRO81169  
Figure 1065: DNA325749, NP\_003868.1, 203372.s\_at  
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Figure 1067: DNA325749, STAT2, 203373.at

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 Figure 1071: DNA151022, NP\_001336.1, 203385.at  
 Figure 1072: PRO12096  
 Figure 1073: DNA331460, NP\_002780.1, 203396.at  
 Figure 1074: PRO60499  
 Figure 1075: DNA326892, NP\_003711.1, 203405.at  
 Figure 1076: PRO83213  
 Figure 1077: DNA274778, NP\_005917.1, 203406.at  
 Figure 1078: PRO62545  
 Figure 1079: DNA270134, NP\_000098.1, 203409.at  
 Figure 1080: PRO58523  
 Figure 1081: DNA28759, NP\_006150.1, 203413.at  
 Figure 1082: PRO2520  
 Figure 1083: DNA287267, NP\_001228.1, 203418.at  
 Figure 1084: PRO37015  
 Figure 1085A-B: DNA256807, NP\_057339.1, 203420.at  
 Figure 1086: PRO51738  
 Figure 1087: DNA326745, NP\_002682.1, 203422.at  
 Figure 1088: PRO83083  
 Figure 1089: DNA330009, NP\_054753.1, 203428.s.at  
 Figure 1090: PRO85297  
 Figure 1091A-B: DNA275186, DNA275186, 203432.at  
 Figure 1092A-B: DNA330010, NP\_005721.2, 203445.s.at  
 Figure 1093: PRO85298  
 Figure 1094: DNA273410, NP\_004036.1, 203454.s.at  
 Figure 1095: PRO61409  
 Figure 1096: DNA328495, NP\_055578.1, 203465.at  
 Figure 1097: PRO58967  
 Figure 1098A-C: DNA331461, NP\_005493.2, 203504.s.at  
 Figure 1099: PRO86511  
 Figure 1100A-B: DNA331462, NP\_003096.1, 203509.at  
 Figure 1101: PRO86512  
 Figure 1102: DNA272911, NP\_006545.1, 203517.at  
 Figure 1103: PRO60997  
 Figure 1104A-D: DNA331463, NP\_000072.1, 203518.at  
 Figure 1105: PRO86513  
 Figure 1106A-C: DNA331464, NP\_055160.1, 203520.s.at  
 Figure 1107: PRO86514  
 Figure 1108A-C: DNA330014, HRIHFB2436, 203521.s.at  
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 Figure 1111: PRO81936  
 Figure 1112: DNA323910, NP\_002956.1, 203535.at  
 Figure 1113: PRO80648  
 Figure 1114A-B: DNA272399, NP\_001197.1, 203542.s.at  
 Figure 1115: PRO60653  
 Figure 1116A-B: DNA272399, BTEB1, 203543.s.at  
 Figure 1117: PRO60653  
 Figure 1118: DNA324684, NP\_004210.1, 203554.x.at  
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 Figure 1120: DNA330015, NP\_004620.1, 203564.at  
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 Figure 1122: DNA330016, NP\_006346.1, 203567.s.at  
 Figure 1123: PRO85303  
 Figure 1124A-B: DNA150765, NP\_003974.1, 203579.s.at  
 Figure 1125: PRO12458  
 Figure 1126: DNA273676, NP\_055488.1, 203584.at  
 Figure 1127: PRO61644  
 Figure 1128: DNA271003, NP\_003720.1, 203594.at  
 Figure 1129: PRO59332  
 Figure 1130A-B: DNA270323, NP\_036552.1, 203595.s.at  
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 Figure 1132A-B: DNA270323, RI58, 203596.s.at  
 Figure 1133: PRO58710  
 Figure 1134: DNA330017, NP\_009118.1, 203597.s.at  
 Figure 1135: PRO60916  
 Figure 1136: DNA329604, NP\_003127.1, 203605.at  
 Figure 1137: PRO85134  
 Figure 1138: DNA287246, NP\_004044.2, 203612.at  
 Figure 1139: PRO69521  
 Figure 1140: DNA330018, NP\_064528.1, 203622.s.at  
 Figure 1141: PRO85304  
 Figure 1142: DNA331465, SKP2, 203625.x.at  
 Figure 1143: PRO81225  
 Figure 1144A-B: DNA327596, 345314.2, 203628.at  
 Figure 1145: PRO1920  
 Figure 1146A-B: DNA331466, BCL2, 203685.at  
 Figure 1147: PRO86515  
 Figure 1148A-B: DNA330021, NP\_001940.1, 203693.s.at  
 Figure 1149: PRO85306  
 Figure 1150: DNA329900, RFC2, 203696.s.at  
 Figure 1151: PRO81549  
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 Figure 1154: DNA329144, KIAA0020, 203712.at  
 Figure 1155: PRO84779  
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 Figure 1157: PRO82793  
 Figure 1158: DNA324183, DPP4, 203716.s.at  
 Figure 1159: PRO80881  
 Figure 1160: DNA150784, NP\_001974.1, 203720.s.at  
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 Figure 1162A-B: DNA269573, NP\_002212.1, 203723.at  
 Figure 1163: PRO57986  
 Figure 1164: DNA330023, NP\_001915.1, 203725.at  
 Figure 1165: PRO85308

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Figure 1169: PRO81905  
Figure 1170A-B: DNA150748, NP\_001105.1, 203741\_s.at  
Figure 1171: PRO12446  
Figure 1172: DNA327523, AQP3, 203747\_at  
Figure 1173: PRO38028  
Figure 1174: DNA330024, NP\_058521.1, 203748\_x.at  
Figure 1175: PRO85309  
Figure 1176: DNA97279, NP\_005345.2, 203751\_x.at  
Figure 1177: PRO3628  
Figure 1178A-B: DNA325972, BUB1B, 203755\_at  
Figure 1179: PRO82417  
Figure 1180: DNA330025, NP\_055565.2, 203764\_at  
Figure 1181: PRO85310  
Figure 1182: DNA330026, NP\_005899.1, 203778\_at  
Figure 1183: PRO85311  
Figure 1184: DNA330027, NP\_036578.1, 203787\_at  
Figure 1185: PRO85312  
Figure 1186A-B: DNA150954, NP\_055695.1, 203799\_at  
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Figure 1188: DNA331468, DGUOK, 203816\_at  
Figure 1189: PRO86517  
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Figure 1191: PRO62061  
Figure 1192A-B: DNA331469, 094680.4, 203845\_at  
Figure 1193: PRO86518  
Figure 1194A-B: DNA325529, GAB2, 203853\_s.at  
Figure 1195: PRO82037  
Figure 1196A-B: DNA275079, NP\_056648.1, 203865\_s.at  
Figure 1197: PRO62797  
Figure 1198: DNA275339, NP\_005685.1, 203880\_at  
Figure 1199: PRO63012  
Figure 1200: DNA329034, NP\_006075.2, 203882\_at  
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Figure 1202A-B: DNA288692, NP\_055719.1, 203884\_s.at  
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Figure 1204: DNA328513, TAF9, 203893\_at  
Figure 1205: PRO37815  
Figure 1206A-B: DNA330030, NP\_055684.1, 203907\_s.at  
Figure 1207: PRO85315  
Figure 1208: DNA82376, NP\_002407.1, 203915\_at  
Figure 1209: PRO1723  
Figure 1210: DNA271676, NP\_002052.1, 203925\_at  
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Figure 1212: DNA288249, NP\_002940.1, 203931\_s.at  
Figure 1213: PRO69507  
Figure 1214: DNA330031, NP\_057210.1, 203960\_s.at  
Figure 1215: PRO85316

Figure 1216: DNA275012, NP\_004679.1, 203964\_at  
Figure 1217: PRO62740  
Figure 1218: DNA272338, NP\_001245.1, 203967\_at  
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Figure 1220: DNA272338, CDC6, 203968\_s.at  
Figure 1221: PRO60595  
Figure 1222: DNA227232, NP\_001850.1, 203971\_at  
Figure 1223: PRO37695  
Figure 1224: DNA271374, NP\_005474.1, 203976\_s.at  
Figure 1225: PRO59673  
Figure 1226: DNA226133, NP\_001983.1, 203989\_x.at  
Figure 1227: PRO36596  
Figure 1228: DNA225915, NP\_000561.1, 204006\_s.at  
Figure 1229: PRO36378  
Figure 1230: DNA330032, HUMGCRFC, 204007\_at  
Figure 1231: PRO85317  
Figure 1232: DNA329145, DUSP4, 204014\_at  
Figure 1233: PRO84780  
Figure 1234: DNA331470, HSU48807, 204015\_s.at  
Figure 1235: PRO86519  
Figure 1236: DNA326089, NP\_000508.1, 204018\_x.at  
Figure 1237: PRO3629  
Figure 1238: DNA330033, NP\_056492.1, 204019\_s.at  
Figure 1239: PRO85318  
Figure 1240: DNA330034, NP\_002907.1, 204023\_at  
Figure 1241: PRO85319  
Figure 1242: DNA328271, NP\_008988.2, 204026\_s.at  
Figure 1243: PRO81868  
Figure 1244: DNA330035, NP\_004228.1, 204033\_at  
Figure 1245: PRO85320  
Figure 1246: DNA325181, CLTA, 204050\_s.at  
Figure 1247: PRO81742  
Figure 1248: DNA226342, NP\_000305.1, 204054\_at  
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Figure 1250A-B: DNA331471, NP\_055498.1, 204063\_s.at  
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Figure 1252: DNA274783, NP\_006272.1, 204068\_at  
Figure 1253: PRO62549  
Figure 1254A-C: DNA331472, NP\_075463.1, 204072\_s.at  
Figure 1255: PRO86520  
Figure 1256: DNA270476, NP\_003591.1, 204092\_s.at  
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Figure 1258: DNA216689, NP\_002975.1, 204103\_at  
Figure 1259: PRO34276  
Figure 1260: DNA328522, NP\_001769.2, 204118\_at  
Figure 1261: PRO2696  
Figure 1262: DNA150529, NP\_003323.1, 204122\_at  
Figure 1263: PRO12313  
Figure 1264: DNA328524, NP\_057097.1, 204125\_at  
Figure 1265: PRO84336  
Figure 1266: DNA304489, NP\_003495.1, 204126\_s.at  
Figure 1267: PRO71058  
Figure 1268: DNA330037, BC000149, 204127\_at  
Figure 1269: PRO82290

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 Figure 1274: DNA103532, NP\_003263.1, 204137.at  
 Figure 1275: PRO4859  
 Figure 1276: DNA330038, BC016330, 204146.at  
 Figure 1277: PRO85322  
 Figure 1278: DNA330039, NP\_002396.2, 204152.s\_at  
 Figure 1279: PRO85323  
 Figure 1280: DNA330039, MFNG, 204153.s\_at  
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 Figure 1282: DNA330040, NP\_523240.1, 204159.at  
 Figure 1283: PRO59546  
 Figure 1284: DNA273694, NP\_006092.1, 204162.at  
 Figure 1285: PRO61661  
 Figure 1286: DNA227116, NP\_006738.1, 204164.at  
 Figure 1287: PRO37579  
 Figure 1288A-B: DNA254376, NP\_055778.1, 204166.at  
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 Figure 1290: DNA272655, NP\_001818.1, 204170.s\_at  
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 Figure 1292: DNA330041, NP\_000088.2, 204172.at  
 Figure 1293: PRO85324  
 Figure 1294: DNA328528, MLC1SA, 204173.at  
 Figure 1295: PRO60636  
 Figure 1296: DNA329148, NP\_056955.1, 204175.at  
 Figure 1297: PRO84782  
 Figure 1298: DNA226380, NP\_001765.1, 204192.at  
 Figure 1299: PRO4695  
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 Figure 1301: PRO60062  
 Figure 1302: DNA330042, HSU16307, 204221.x\_at  
 Figure 1303: PRO85325  
 Figure 1304: DNA150812, NP\_006842.1, 204222.s\_at  
 Figure 1305: PRO12481  
 Figure 1306: DNA227514, NP\_000152.1, 204224.s\_at  
 Figure 1307: PRO37977  
 Figure 1308: DNA88308, NP\_004097.1, 204232.at  
 Figure 1309: PRO2739  
 Figure 1310: DNA226881, NP\_002008.2, 204236.at  
 Figure 1311: PRO37344  
 Figure 1312: DNA270434, NP\_006434.1, 204238.s\_at  
 Figure 1313: PRO58814  
 Figure 1314A-B: DNA287273, NP\_006435.1, 204240.s\_at  
 Figure 1315: PRO69545  
 Figure 1316: DNA330043, NP\_001789.2, 204252.at  
 Figure 1317: PRO85326  
 Figure 1318A-B: DNA103527, NP\_000367.1, 204253.s\_at  
 Figure 1319: PRO4854  
 Figure 1320A-B: DNA103527, VDR, 204254.s\_at  
 Figure 1321: PRO4854  
 Figure 1322A-B: DNA103527, HUMVDR, 204255.s\_at  
 Figure 1323: PRO4854  
 Figure 1324: DNA228132, NP\_076995.1, 204256.at  
 Figure 1325: PRO38595  
 Figure 1326: DNA226577, NP\_071390.1, 204265.s\_at  
 Figure 1327: PRO37040  
 Figure 1328: DNA88643, SGSH, 204293.at  
 Figure 1329: PRO2455  
 Figure 1330: DNA330044, GTSE1, 204318.s\_at  
 Figure 1331: PRO85327  
 Figure 1332: DNA330045, NP\_005943.1, 204326.x\_at  
 Figure 1333: PRO82583  
 Figure 1334: DNA328530, NP\_009198.2, 204328.at  
 Figure 1335: PRO24118  
 Figure 1336: DNA330046, 987987.10, 204334.at  
 Figure 1337: PRO85328  
 Figure 1338: DNA328531, NP\_037542.1, 204348.s\_at  
 Figure 1339: PRO84338  
 Figure 1340: DNA330047, BC005250, 204349.at  
 Figure 1341: PRO37777  
 Figure 1342A-B: DNA193847, NP\_055518.1, 204377.s\_at  
 Figure 1343: PRO23272  
 Figure 1344: DNA328533, NP\_003647.1, 204392.at  
 Figure 1345: PRO84340  
 Figure 1346: DNA226462, NP\_002241.1, 204401.at  
 Figure 1347: PRO36925  
 Figure 1348A-B: DNA330048, AF080255, 204407.at  
 Figure 1349: PRO85329  
 Figure 1350: DNA327616, NP\_075011.1, 204415.at  
 Figure 1351: PRO83624  
 Figure 1352: DNA331473, NP\_000839.1, 204418.x\_at  
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 Figure 1355: PRO36749  
 Figure 1356: DNA327617, NP\_006811.1, 204439.at  
 Figure 1357: PRO83625  
 Figure 1358A-B: DNA330049, NP\_004514.2, 204444.at  
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 Figure 1360: DNA329150, NP\_000689.1, 204446.s\_at  
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 Figure 1362: DNA270496, NP\_001316.1, 204459.at  
 Figure 1363: PRO58875  
 Figure 1364: DNA330050, NP\_056289.1, 204502.at  
 Figure 1365: PRO85331  
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 Figure 1367: PRO61586  
 Figure 1368: DNA330051, NP\_003431.1, 204523.at  
 Figure 1369: PRO85332  
 Figure 1370A-B: DNA330052, NP\_009227.1, 204531.s\_at  
 Figure 1371: PRO25103  
 Figure 1372: DNA82362, NP\_001556.1, 204533.at  
 Figure 1373: PRO1718  
 Figure 1374A-B: DNA331474, 357276.11, 204552.at

Figure 1375: PRO86521  
 Figure 1376A-B: DNA329036, NP\_002451.1, 204562.at  
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 Figure 1378: DNA287284, NP\_060943.1, 204565.at  
 Figure 1379: PRO59915  
 Figure 1380: DNA151910, NP\_004906.2, 204567.s.at  
 Figure 1381: PRO12754  
 Figure 1382A-B: DNA273627, NP\_055739.1, 204568.at  
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 Figure 1384: DNA272992, N4BP1, 204601.at  
 Figure 1385: PRO61064  
 Figure 1386: DNA254157, NP\_005245.2, 204618.s.at  
 Figure 1387: PRO49271  
 Figure 1388: DNA151048, NP\_006177.1, 204621.s.at  
 Figure 1389: PRO12850  
 Figure 1390: DNA151048, NR4A2, 204622.x.at  
 Figure 1391: PRO12850  
 Figure 1392A-B: DNA330054, NP\_004746.1, 204633.s.at  
 Figure 1393: PRO85334  
 Figure 1394: DNA254470, NP\_002488.1, 204641.at  
 Figure 1395: PRO49578  
 Figure 1396: DNA226182, EDG1, 204642.at  
 Figure 1397: PRO36645  
 Figure 1398: DNA210121, CDW52, 204661.at  
 Figure 1399: PRO33667  
 Figure 1400: DNA103526, LRMP, 204674.at  
 Figure 1401: PRO4853  
 Figure 1402: DNA225974, NP\_000864.1, 204683.at  
 Figure 1403: PRO36437  
 Figure 1404: DNA256295, LRN, 204692.at  
 Figure 1405: PRO51339  
 Figure 1406: DNA227573, NP\_001780.1, 204696.s.at  
 Figure 1407: PRO38036  
 Figure 1408: DNA329151, NP\_004280.3, 204702.s.at  
 Figure 1409: PRO84784  
 Figure 1410: DNA331475, KNLS5, 204709.s.at  
 Figure 1411: PRO86522  
 Figure 1412A-B: DNA331476, NP\_000121.1, 204713.s.at  
 Figure 1413: PRO86523  
 Figure 1414A-B: DNA225911, F5, 204714.s.at  
 Figure 1415: PRO36374  
 Figure 1416A-B: DNA218283, NP\_004436.1, 204718.at  
 Figure 1417: PRO34335  
 Figure 1418A-B: DNA256461, NP\_009017.1, 204728.s.at  
 Figure 1419: PRO51498  
 Figure 1420A-C: DNA274487, NP\_055562.1, 204730.at  
 Figure 1421: PRO62389  
 Figure 1422A-B: DNA83176, NP\_003234.1, 204731.at  
 Figure 1423: PRO2620  
 Figure 1424A-B: DNA325192, NP\_038203.1, 204744.s.at  
 Figure 1425: PRO81753  
 Figure 1426: DNA330057, NP\_005941.1, 204745.x.at  
 Figure 1427: PRO85337  
 Figure 1428: DNA287178, NP\_001540.1, 204747.at  
 Figure 1429: PRO69467  
 Figure 1430: DNA330058, NP\_004529.2, 204749.at  
 Figure 1431: PRO85338  
 Figure 1432: DNA329153, NP\_001259.1, 204759.at  
 Figure 1433: PRO84786  
 Figure 1434: DNA330059, NP\_068370.1, 204760.s.at  
 Figure 1435: PRO85339  
 Figure 1436: DNA330060, NP\_002443.2, 204766.s.at  
 Figure 1437: PRO85340  
 Figure 1438: DNA329154, BC000323, 204767.s.at  
 Figure 1439: PRO69568  
 Figure 1440: DNA325479, NP\_004102.1, 204768.s.at  
 Figure 1441: PRO69568  
 Figure 1442: DNA328541, NP\_004503.1, 204773.at  
 Figure 1443: PRO4843  
 Figure 1444: DNA329155, NP\_000034.1, 204780.s.at  
 Figure 1445: PRO1207  
 Figure 1446: DNA329155, TNFRSF6, 204781.s.at  
 Figure 1447: PRO1207  
 Figure 1448: DNA272121, NP\_005895.1, 204790.at  
 Figure 1449: PRO60391  
 Figure 1450A-B: DNA330061, NP\_055525.1, 204793.at  
 Figure 1451: PRO85341  
 Figure 1452: DNA103269, NP\_005366.1, 204798.at  
 Figure 1453: PRO4599  
 Figure 1454: DNA287168, NP\_003132.2, 204804.at  
 Figure 1455: PRO69460  
 Figure 1456: DNA330062, NP\_006017.1, 204805.s.at  
 Figure 1457: PRO85342  
 Figure 1458A-B: DNA329907, ESPL1, 204817.at  
 Figure 1459: PRO85224  
 Figure 1460: DNA331477, NP\_003309.1, 204822.at  
 Figure 1461: PRO58276  
 Figure 1462: DNA255289, NP\_055606.1, 204825.at  
 Figure 1463: PRO50363  
 Figure 1464A-B: DNA226387, NP\_001752.1, 204826.at  
 Figure 1465: PRO36850  
 Figure 1466: DNA328544, NP\_006673.1, 204834.at  
 Figure 1467: PRO84347  
 Figure 1468A-B: DNA270446, NP\_058633.1, 204835.at  
 Figure 1469: PRO58825  
 Figure 1470: DNA330063, HUMLPTPASE, 204852.s.at  
 Figure 1471: PRO85343  
 Figure 1472: DNA150598, NP\_003541.1, 204857.at  
 Figure 1473: PRO12142  
 Figure 1474: DNA225661, NP\_001944.1, 204858.s.at

Figure 1475: PRO36124  
Figure 1476A-B: DNA330064, 332518.2, 204886.at  
Figure 1477: PRO85344  
Figure 1478: DNA330065, NP\_055079.2, 204887.s.at  
Figure 1479: PRO85345  
Figure 1480: DNA103444, LCK, 204890.s.at  
Figure 1481: PRO4771  
Figure 1482: DNA331478, BC013200, 204891.s.at  
Figure 1483: PRO86524  
Figure 1484: DNA194139, DNA194139, 204897.at  
Figure 1485: PRO23533  
Figure 1486: DNA255326, NP\_003855.1, 204900.x.at  
Figure 1487: PRO50396  
Figure 1488: DNA329157, NP\_004271.1, 204905.s.at  
Figure 1489: PRO62861  
Figure 1490: DNA329011, NP\_005169.1, 204908.s.at  
Figure 1491: PRO4785  
Figure 1492A-B: DNA76503, NP\_001549.1, 204912.at  
Figure 1493: PRO2536  
Figure 1494: DNA330066, NP\_004520.1, 204917.s.at  
Figure 1495: PRO85346  
Figure 1496: DNA228014, NP\_002153.1, 204949.at  
Figure 1497: PRO38477  
Figure 1498: DNA271093, NP\_004064.1, 204958.at  
Figure 1499: PRO59417  
Figure 1500: DNA103283, NP\_002423.1, 204959.at  
Figure 1501: PRO4613  
Figure 1502: DNA330067, NP\_001800.1, 204962.s.at  
Figure 1503: PRO60368  
Figure 1504: DNA287399, NP\_058197.1, 204972.at  
Figure 1505: PRO69656  
Figure 1506: DNA269665, NP\_002454.1, 204994.at  
Figure 1507: PRO58076  
Figure 1508: DNA331479, 411441.5, 204995.at  
Figure 1509: PRO86525  
Figure 1510: DNA272427, NP\_004799.1, 205005.s.at  
Figure 1511: PRO60679  
Figure 1512: DNA272427, NMT2, 205006.s.at  
Figure 1513: PRO60679  
Figure 1514: DNA329534, NP\_004615.2, 205019.s.at  
Figure 1515: PRO2904  
Figure 1516: DNA331480, RAD51, 205024.s.at  
Figure 1517: PRO86526  
Figure 1518: DNA329159, NP\_005195.2, 205027.s.at  
Figure 1519: PRO4660  
Figure 1520: DNA325061, NP\_005208.1, 205033.s.at  
Figure 1521: PRO9980  
Figure 1522: DNA328297, NP\_477097.1, 205034.at  
Figure 1523: PRO59418  
Figure 1524A-C: DNA331481, NP\_001804.1, 205046.at  
Figure 1525: PRO86527  
Figure 1526: DNA324991, ASNS, 205047.s.at  
Figure 1527: PRO81585  
Figure 1528: DNA271461, NP\_000937.1, 205053.at  
Figure 1529: PRO59757  
Figure 1530A-B: DNA220750, NP\_002199.2, 205055.at  
Figure 1531: PRO34728  
Figure 1532: DNA330071, NP\_003607.1, 205063.at  
Figure 1533: PRO85350  
Figure 1534: DNA330072, NP\_071801.1, 205072.s.at  
Figure 1535: PRO85351  
Figure 1536: DNA304705, NP\_002634.1, 205078.at  
Figure 1537: PRO71131  
Figure 1538: DNA327632, NP\_001302.1, 205081.at  
Figure 1539: PRO83635  
Figure 1540: DNA255336, NP\_061332.1, 205084.at  
Figure 1541: PRO50406  
Figure 1542: DNA330073, NP\_004144.1, 205085.at  
Figure 1543: PRO85352  
Figure 1544: DNA330074, HUMHM145, 205098.at  
Figure 1545: PRO85353  
Figure 1546: DNA226177, NP\_001286.1, 205099.s.at  
Figure 1547: PRO36640  
Figure 1548: DNA192060, NP\_002974.1, 205114.s.at  
Figure 1549: PRO21960  
Figure 1550: DNA299899, NP\_002148.1, 205133.s.at  
Figure 1551: PRO62760  
Figure 1552: DNA331482, NP\_001241.1, 205153.s.at  
Figure 1553: PRO34457  
Figure 1554: DNA330075, CDC25C, 205167.s.at  
Figure 1555: PRO85354  
Figure 1556: DNA330076, NP\_005410.1, 205170.at  
Figure 1557: PRO85355  
Figure 1558: DNA328810, NP\_001770.1, 205173.x.at  
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Figure 1565: PRO60693  
Figure 1566: DNA273535, NP\_004217.1, 205214.at  
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Figure 1569: PRO1910  
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Figure 1571: PRO46  
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Figure 1574: DNA188333, NP\_006410.1, 205242.at  
Figure 1575: PRO21708  
Figure 1576: DNA227081, NP\_000390.2, 205249.at  
Figure 1577: PRO37544  
Figure 1578: DNA227447, NP\_003193.1, 205254.x.at  
Figure 1579: PRO37910  
Figure 1580: DNA227447, TCF7, 205255.x.at  
Figure 1581: PRO37910  
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Figure 1583: PRO36946

Figure 1584A-B: DNA330079, 341358.1, 205263\_at  
Figure 1585: PRO1162  
Figure 1586A-B: DNA188301, NP\_002300.1, 205266\_at  
Figure 1587: PRO21834  
Figure 1588: DNA227173, NP\_001456.1, 205285\_s.at  
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Figure 1591: PRO86528  
Figure 1592A-B: DNA331484, NP\_000869.1, 205291\_at  
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Figure 1594: DNA88119, NP\_000617.1, 205297\_s.at  
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Figure 1596A-B: DNA330081, NP\_003026.1, 205339\_at  
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Figure 1598: DNA256854, NP\_000456.1, 205345\_at  
Figure 1599: PRO51785  
Figure 1600: DNA270415, NP\_002059.1, 205349\_at  
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Figure 1604: DNA325568, CHEK1, 205394\_at  
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Figure 1608: DNA328561, NP\_004624.1, 205403\_at  
Figure 1609: PRO2019  
Figure 1610: DNA329010, NP\_004942.1, 205419\_at  
Figure 1611: PRO23370  
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Figure 1614: DNA287337, NP\_002096.1, 205436\_s.at  
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Figure 1619: PRO60483  
Figure 1620: DNA88194, NP\_000724.1, 205456\_at  
Figure 1621: PRO2220  
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Figure 1629: PRO36422  
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Figure 1644: DNA330087, PCSK5, 205559\_s.at  
Figure 1645: PRO85361  
Figure 1646: DNA256257, NP\_055213.1, 205569\_at  
Figure 1647: PRO51301  
Figure 1648A-B: DNA327643, NP\_055712.1, 205594\_at  
Figure 1649: PRO83644  
Figure 1650: DNA329013, NP\_005649.1, 205599\_at  
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Figure 1652: DNA324324, NP\_000679.1, 205633\_s.at  
Figure 1653: PRO81000  
Figure 1654: DNA330088, NP\_003087.1, 205644\_s.at  
Figure 1655: PRO61962  
Figure 1656: DNA287317, NP\_003724.1, 205660\_at  
Figure 1657: PRO69582  
Figure 1658: DNA328570, NP\_004040.1, 205681\_at  
Figure 1659: PRO37843  
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Figure 1667: PRO34739  
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Figure 1672: DNA331318, SLC27A2, 205769\_at  
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Figure 1676: DNA330092, NP\_004904.1, 205781\_at  
Figure 1677: PRO85363  
Figure 1678A-B: DNA220752, NP\_000623.1, 205786\_s.at  
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Figure 1705: PRO4940  
Figure 1706: DNA287318, NP\_002683.1, 205909.at  
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Figure 1710: DNA76516, NP\_000556.1, 205945.at  
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Figure 1713: PRO58425  
Figure 1714: DNA273487, NP\_004785.1, 206039.at  
Figure 1715: PRO61470  
Figure 1716A-B: DNA290265, NP\_003421.1, 206059.at  
Figure 1717: PRO70395  
Figure 1718: DNA330096, NP\_057051.1, 206060.s.at  
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Figure 1720: DNA271992, NP\_006665.1, 206082.at  
Figure 1721: PRO60267  
Figure 1722: DNA270851, NP\_006617.1, 206098.at  
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Figure 1724: DNA226105, NP\_002925.1, 206111.at  
Figure 1725: PRO36568  
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Figure 1727: PRO2068  
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Figure 1737: PRO12612  
Figure 1738: DNA330098, NP\_073619.1, 206205.at  
Figure 1739: PRO85367

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Figure 1744: DNA281446, GAP1IP4BP, 206221.at  
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Figure 1752: DNA269870, NP\_005382.1, 206348.s.at  
Figure 1753: PRO58270  
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Figure 1755: PRO85369  
Figure 1756: DNA329169, NP\_002986.1, 206366.x.at  
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Figure 1759: PRO59617  
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Figure 1768: DNA88203, NP\_055022.1, 206485.at  
Figure 1769: PRO2698  
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Figure 1771: PRO36451  
Figure 1772: DNA269850, NP\_002003.1, 206492.at  
Figure 1773: PRO58251  
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Figure 1783: PRO38003  
Figure 1784: DNA330103, NP\_056179.1, 206584.at  
Figure 1785: PRO19671  
Figure 1786: DNA329172, NP\_005254.1, 206589.at  
Figure 1787: PRO84796  
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Figure 1789: PRO4778

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 Figure 1799: PRO85372  
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 Figure 1803: PRO85373  
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 Figure 1805: PRO2691  
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 Figure 1813: PRO51592  
 Figure 1814: DNA93439, NP\_006555.1, 206974.at  
 Figure 1815: PRO4515  
 Figure 1816: DNA35629, NP\_000586.2, 206975.at  
 Figure 1817: PRO7  
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 Figure 1820: DNA331493, CCR2, 206978.at  
 Figure 1821: PRO84690  
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 Figure 1823: PRO21766  
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 Figure 1825: PRO38122  
 Figure 1826A-B: DNA227750, NP\_001550.1, 206999.at  
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 Figure 1828: DNA329903, PPP3CC, 207000.s.at  
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 Figure 1833: PRO62736  
 Figure 1834: DNA331495, HUMBCL2B, 207005.s.at  
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 Figure 1838: DNA225550, NP\_003844.1, 207072.at  
 Figure 1839: PRO36013  
 Figure 1840: DNA273159, NP\_005457.1, 207078.at  
 Figure 1841: PRO61201  
 Figure 1842: DNA227481, VAMP1, 207100.s.at  
 Figure 1843: PRO37944  
 Figure 1844: DNA218655, NP\_000585.1, 207113.s.at  
 Figure 1845: PRO34451  
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 Figure 1853: PRO85377  
 Figure 1854: DNA330114, NP\_006134.1, 207183.at  
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 Figure 1859: PRO2057  
 Figure 1860A-B: DNA330115, NP\_077739.1, 207324.s.at  
 Figure 1861: PRO85378  
 Figure 1862A-B: DNA226536, NP\_003225.1, 207332.s.at  
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 Figure 1864: DNA331497, LTB, 207339.s.at  
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 Figure 1867: PRO85379  
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 Figure 1869: PRO85380  
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 Figure 1871: PRO36859  
 Figure 1872: DNA227668, NP\_000158.1, 207387.s.at  
 Figure 1873: PRO38131  
 Figure 1874A-B: DNA329093, MSF, 207425.s.at  
 Figure 1875: PRO84745  
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 Figure 1877: PRO73  
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 Figure 1882: DNA328597, ATP5G3, 207508.at  
 Figure 1883: PRO84381  
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 Figure 1886A-B: DNA256059, ATP2A3, 207522.s.at  
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 Figure 1891: PRO81977  
 Figure 1892: DNA328601, NP\_056490.1, 207574.s.at  
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 Figure 1894A-B: DNA330120, FLJ10971, 207606.s.at  
 Figure 1895: PRO85382

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 Figure 1899: PRO86535  
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 Figure 1901: PRO36800  
 Figure 1902: DNA227606, NP\_001872.2, 207630.s\_at  
 Figure 1903: PRO38069  
 Figure 1904: DNA196426, NP\_037440.1, 207651.at  
 Figure 1905: PRO24924  
 Figure 1906: DNA328554, NP\_038202.1, 207677.s\_at  
 Figure 1907: PRO84354  
 Figure 1908A-B: DNA226405, NP\_006525.1, 207700.s\_at  
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 Figure 1910: DNA329064, NP\_060301.1, 207735.at  
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 Figure 1912: DNA329020, NUP62, 207740.s\_at  
 Figure 1913: PRO84695  
 Figure 1914: DNA325654, NP\_054752.1, 207761.s\_at  
 Figure 1915: PRO4348  
 Figure 1916A-B: DNA329179, NP\_056958.1, 207785.s\_at  
 Figure 1917: PRO84802  
 Figure 1918: DNA227494, NP\_002158.1, 207826.s\_at  
 Figure 1919: PRO37957  
 Figure 1920A-C: DNA331499, NP\_057427.2, 207828.s\_at  
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 Figure 1923: PRO84805  
 Figure 1924: DNA330123, NP\_008984.1, 207840.at  
 Figure 1925: PRO35080  
 Figure 1926: DNA227175, NP\_006857.1, 207857.at  
 Figure 1927: PRO37638  
 Figure 1928: DNA330124, NP\_002981.2, 207861.at  
 Figure 1929: PRO34107  
 Figure 1930: DNA217245, NP\_000579.1, 207906.at  
 Figure 1931: PRO34287  
 Figure 1932: DNA218651, NP\_003798.1, 207907.at  
 Figure 1933: PRO34447  
 Figure 1934: DNA330125, NP\_002729.2, 207957.s\_at  
 Figure 1935: PRO85385  
 Figure 1936A-B: DNA226290, NP\_036333.1, 207966.s\_at  
 Figure 1937: PRO36753  
 Figure 1938: DNA329183, NP\_055962.1, 207971.s\_at  
 Figure 1939: PRO84806  
 Figure 1940A-B: DNA330126, NP\_008912.1, 207978.s\_at  
 Figure 1941: PRO85386  
 Figure 1942: DNA329184, CITED2, 207980.s\_at  
 Figure 1943: PRO84807  
 Figure 1944A-C: DNA254145, NP\_004329.1, 207996.s\_at  
 Figure 1945: PRO49260  
 Figure 1946: DNA275286, NP\_009205.1, 208002.s\_at  
 Figure 1947: PRO62967  
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 Figure 1949: PRO69990  
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 Figure 1952A-B: DNA188492, NAB1, 208047.s\_at  
 Figure 1953: PRO22070  
 Figure 1954: DNA330127, NP\_006442.2, 208051.s\_at  
 Figure 1955: PRO85387  
 Figure 1956A-B: DNA328607, NP\_003639.1, 208072.s\_at  
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 Figure 1958A-C: DNA331500, NP\_003307.2, 208073.x\_at  
 Figure 1959: PRO86537  
 Figure 1960A-B: DNA328312, NP\_110378.1, 208078.s\_at  
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 Figure 1963: PRO58855  
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 Figure 1965: PRO80638  
 Figure 1966: DNA330129, NP\_112495.1, 208119.s\_at  
 Figure 1967: PRO85389  
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 Figure 1969: PRO81872  
 Figure 1970: DNA36717, NP\_000581.1, 208193.at  
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 Figure 1972A-E: DNA330130, HSTTTIN, 208195.at  
 Figure 1973: DNA328611, RASGRP2, 208206.s\_at  
 Figure 1974: PRO84393  
 Figure 1975: DNA328612, NP\_000166.2, 208308.s\_at  
 Figure 1976: PRO84394  
 Figure 1977A-D: DNA331502, NP\_000050.1, 208368.s\_at  
 Figure 1978: PRO86538  
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 Figure 1981A-B: DNA331503, RAD50, 208393.s\_at  
 Figure 1982: PRO86539  
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 Figure 1984: PRO83673  
 Figure 1985: DNA103427, NP\_005239.1, 208438.s\_at  
 Figure 1986: PRO4755  
 Figure 1987A-C: DNA331504, ATM, 208442.s\_at  
 Figure 1988: PRO86540  
 Figure 1989A-B: DNA330134, BAZ1B, 208445.s\_at  
 Figure 1990: PRO85394  
 Figure 1991A-C: DNA331505, NP\_000642.2, 208488.s\_at  
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 Figure 1994: PRO82583  
 Figure 1995A-C: DNA331506, NP\_001448.1, 208614.s\_at

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 Figure 2001A-B: DNA273567, EIF4G1, 208625.s\_at  
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 Figure 2004: PRO82367  
 Figure 2005: DNA325912, ACTN1, 208637.x\_at  
 Figure 2006: PRO82367  
 Figure 2007: DNA329188, BC012142, 208638.at  
 Figure 2008: PRO84810  
 Figure 2009: DNA324641, NP\_005608.1, 208646.at  
 Figure 2010: PRO10849  
 Figure 2011: DNA271268, NP\_009057.1, 208649.s\_at  
 Figure 2012: PRO59579  
 Figure 2013: DNA328617, AF299343, 208653.s\_at  
 Figure 2014: PRO84399  
 Figure 2015: DNA330139, AK022493, 208657.s\_at  
 Figure 2016: PRO85398  
 Figure 2017A-C: DNA151898, TTC3, 208661.s\_at  
 Figure 2018: PRO12135  
 Figure 2019A-C: DNA151898, D84294, 208662.s\_at  
 Figure 2020: PRO12135  
 Figure 2021A-C: DNA331507, D83327, 208663.s\_at  
 Figure 2022: DNA304686, NP\_002565.1, 208680.at  
 Figure 2023: PRO71112  
 Figure 2024A-B: DNA328619, BC001188, 208691.at  
 Figure 2025: PRO84401  
 Figure 2026: DNA287189, NP\_002038.1, 208693.s\_at  
 Figure 2027: PRO69475  
 Figure 2028: DNA330140, AF275798, 208696.at  
 Figure 2029: PRO85399  
 Figure 2030A-C: DNA331508, 198777.9, 208707.at  
 Figure 2031: PRO86543  
 Figure 2032: DNA97298, NP\_003899.1, 208726.s\_at  
 Figure 2033: PRO3645  
 Figure 2034: DNA330142, BC003564, 208737.at  
 Figure 2035: PRO85401  
 Figure 2036: DNA331509, 1138554.23, 208740.at  
 Figure 2037: PRO86544  
 Figure 2038: DNA328591, HSP105B, 208744.x\_at  
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 Figure 2040: DNA287285, NP\_005794.1, 208748.s\_at  
 Figure 2041: PRO69556  
 Figure 2042: DNA324217, ATIC, 208758.at  
 Figure 2043: PRO80908  
 Figure 2044: DNA327696, AF228339, 208763.s\_at  
 Figure 2045: PRO83679  
 Figure 2046A-B: DNA331510, 1298307.1, 208776.at  
 Figure 2047: PRO86545  
 Figure 2048: DNA287427, NP\_002806.1, 208777.s\_at  
 Figure 2049: PRO69684  
 Figure 2050: DNA287219, NP\_110379.1, 208778.s\_at  
 Figure 2051: PRO69498  
 Figure 2052: DNA329189, NP\_009139.1, 208787.at  
 Figure 2053: PRO4911  
 Figure 2054: DNA238565, NP\_005907.2, 208795.s\_at  
 Figure 2055: PRO39210  
 Figure 2056: DNA330145, NP\_002788.1, 208799.at  
 Figure 2057: PRO84403  
 Figure 2058: DNA331511, HSMPIO, 208805.at  
 Figure 2059A-C: DNA331512, 1397486.26, 208806.at  
 Figure 2060: PRO86547  
 Figure 2061A-B: DNA330147, HSU91543, 208807.s\_at  
 Figure 2062: PRO85405  
 Figure 2063: DNA324531, NP\_002120.1, 208808.s\_at  
 Figure 2064: PRO81185  
 Figure 2065: DNA273521, NP\_002070.1, 208813.at  
 Figure 2066: PRO61502  
 Figure 2067A-B: DNA330148, AB020636, 208838.at  
 Figure 2068A-B: DNA330149, HSM801778, 208839.s\_at  
 Figure 2069: PRO82209  
 Figure 2070: DNA227874, NP\_003320.1, 208864.s\_at  
 Figure 2071: PRO38337  
 Figure 2072: DNA328624, BC003562, 208891.at  
 Figure 2073: PRO59076  
 Figure 2074: DNA331513, DUSP6, 208892.s\_at  
 Figure 2075: PRO84404  
 Figure 2076: DNA331330, BC005047, 208893.s\_at  
 Figure 2077: PRO82215  
 Figure 2078: DNA329221, NP\_061984.1, 208894.at  
 Figure 2079: PRO4555  
 Figure 2080A-B: DNA329007, NP\_003277.1, 208900.s\_at  
 Figure 2081: PRO37029  
 Figure 2082A-B: DNA329007, TOP1, 208901.s\_at  
 Figure 2083: PRO37029  
 Figure 2084: DNA327700, BC015130, 208905.at  
 Figure 2085: PRO83683  
 Figure 2086: DNA327701, NP\_001203.1, 208910.s\_at  
 Figure 2087: PRO82667  
 Figure 2088: DNA281442, NP\_149124.1, 208912.s\_at  
 Figure 2089: PRO66281  
 Figure 2090A-B: DNA330151, AB029003, 208914.at  
 Figure 2091: DNA325473, NP\_006353.2, 208922.s\_at  
 Figure 2092: PRO81996  
 Figure 2093: DNA329552, NP\_063948.1, 208925.at  
 Figure 2094: PRO85097  
 Figure 2095: DNA326233, NP\_000968.2, 208929.x\_at  
 Figure 2096: PRO82645  
 Figure 2097: DNA327702, NP\_006490.2, 208934.s\_at  
 Figure 2098: PRO83684  
 Figure 2099: DNA330152, NP\_001939.1, 208956.x\_at  
 Figure 2100: PRO85406  
 Figure 2101: DNA290261, NP\_001291.2, 208960.s\_at  
 Figure 2102: PRO70387  
 Figure 2103A-B: DNA325478, NP\_037534.2,

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 Figure 2105: DNA327661, IFI16, 208965.s.at  
 Figure 2106: PRO83652  
 Figure 2107A-B: DNA270277, AF208043, 208966.x.at  
 Figure 2108: PRO58665  
 Figure 2109: DNA326343, KPNB1, 208974.x.at  
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 Figure 2115: DNA330154, HUMPECAM27, 208981.at  
 Figure 2116: DNA330155, 7692317.2, 208982.at  
 Figure 2117: PRO85407  
 Figure 2118: DNA330156, NP\_003749.1, 208985.s.at  
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 Figure 2120: DNA331514, STAT3, 208992.s.at  
 Figure 2121: PRO86548  
 Figure 2122: DNA227552, NP\_003346.2, 208997.s.at  
 Figure 2123: PRO38015  
 Figure 2124: DNA227552, UCP2, 208998.at  
 Figure 2125: PRO38015  
 Figure 2126: DNA328630, NP\_036293.1, 209004.s.at  
 Figure 2127: PRO84408  
 Figure 2128: DNA331515, FBXL5, 209005.at  
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 Figure 2131: PRO84409  
 Figure 2132: DNA331516, DNAJB6, 209015.s.at  
 Figure 2133: PRO83680  
 Figure 2134: DNA328633, NP\_004784.2, 209017.s.at  
 Figure 2135: PRO84411  
 Figure 2136: DNA330158, NP\_057554.4, 209020.at  
 Figure 2137: PRO85410  
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 Figure 2140: DNA328635, BC020946, 209026.x.at  
 Figure 2141: PRO84413  
 Figure 2142: DNA331517, NP\_004150.1, 209040.s.at  
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 Figure 2144A-C: DNA328637, HSA7042, 209052.s.at  
 Figure 2145: PRO81109  
 Figure 2146A-B: DNA331518, AF330040, 209053.s.at  
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 Figure 2148A-B: DNA226405, NCOA3, 209060.x.at  
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 Figure 2154: DNA329194, NP\_112740.1, 209068.at  
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 Figure 2156A-B: DNA330161, NP\_085059.1, 209081.s.at  
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 Figure 2158: DNA330162, NP\_057093.1, 209091.s.at  
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 Figure 2160: DNA330163, NP\_060308.1, 209104.s.at  
 Figure 2161: PRO85415  
 Figure 2162: DNA330164, NP\_004752.1, 209110.s.at  
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 Figure 2164: DNA327709, NP\_000509.1, 209116.x.at  
 Figure 2165: PRO83690  
 Figure 2166: DNA288254, NP\_006000.2, 209118.s.at  
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 Figure 2168: DNA325163, NP\_001113.1, 209122.at  
 Figure 2169: PRO81730  
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 Figure 2173: PRO37975  
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 Figure 2175: PRO81832  
 Figure 2176: DNA330166, BC001588, 209161.at  
 Figure 2177: PRO85418  
 Figure 2178: DNA271722, NP\_004688.1, 209162.s.at  
 Figure 2179: PRO60006  
 Figure 2180: DNA330167, CAB43224.1, 209177.at  
 Figure 2181: PRO85419  
 Figure 2182A-B: DNA328642, AF073310, 209184.s.at  
 Figure 2183: PRO84418  
 Figure 2184: DNA331331, AF161416, 209185.s.at  
 Figure 2185A-B: DNA328643, HUMHK1A, 209186.at  
 Figure 2186: PRO84419  
 Figure 2187: DNA189700, NP\_005243.1, 209189.at  
 Figure 2188: PRO25619  
 Figure 2189: DNA324766, NP\_005443.2, 209196.at  
 Figure 2190: PRO81387  
 Figure 2191: DNA226176, NP\_003458.1, 209201.x.at  
 Figure 2192: PRO36639  
 Figure 2193: DNA326267, NP\_004861.1, 209208.at  
 Figure 2194: PRO82674  
 Figure 2195: DNA326891, NP\_001748.1, 209213.at  
 Figure 2196: PRO83212  
 Figure 2197: DNA227483, NP\_003120.1, 209218.at  
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 Figure 2199: DNA330168, NP\_006322.1, 209233.at  
 Figure 2200: PRO85420  
 Figure 2201: DNA328649, NP\_116093.1, 209251.x.at  
 Figure 2202: PRO84424  
 Figure 2203: DNA255255, NP\_071437.1, 209267.s.at  
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 Figure 2205A-B: DNA188492, AF045451, 209272.at  
 Figure 2206: PRO22070  
 Figure 2207A-B: DNA226827, NP\_001673.1,

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 Figure 2212: PRO82889  
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 Figure 2214: PRO12057  
 Figure 2215: DNA330169, NP\_006709.1, 209318.x.at  
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 Figure 2217: DNA275106, HSU76248, 209339.at  
 Figure 2218: PRO62821  
 Figure 2219: DNA269630, NP\_003281.1, 209344.at  
 Figure 2220: PRO58042  
 Figure 2221A-B: DNA328658, AF055376, 209348.s.at  
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 Figure 2224: PRO84807  
 Figure 2225: DNA327720, NP\_001970.1, 209368.at  
 Figure 2226: PRO83699  
 Figure 2227: DNA330171, CAA34971.1, 209374.s.at  
 Figure 2228: PRO85421  
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 Figure 2230: PRO85422  
 Figure 2231: DNA330173, HUMAUTOTAX, 209392.at  
 Figure 2232: PRO85423  
 Figure 2233: DNA330174, AK027512, 209404.s.at  
 Figure 2234: PRO85424  
 Figure 2235: DNA330175, NP\_006836.1, 209408.at  
 Figure 2236: PRO59681  
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 Figure 2238: PRO59556  
 Figure 2239: DNA330176, AAB61703.1, 209417.s.at  
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 Figure 2245: DNA273076, HSU59863, 209451.at  
 Figure 2246: PRO61137  
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 Figure 2249: DNA287304, AAH00040.1, 209461.x.at  
 Figure 2250: PRO69571  
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 Figure 2252: PRO70812  
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 Figure 2254: PRO85426  
 Figure 2255: DNA330179, NP\_067023.1, 209504.s.at  
 Figure 2256: PRO85427  
 Figure 2257: DNA324899, NP\_002938.1, 209507.at  
 Figure 2258: PRO81503  
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 Figure 2260: PRO85428  
 Figure 2261: DNA274027, RAB27A, 209514.s.at  
 Figure 2262: PRO61971  
 Figure 2263: DNA274027, HSU38654, 209515.s.at  
 Figure 2264: PRO61971  
 Figure 2265: DNA272213, NP\_002477.1, 209520.s.at  
 Figure 2266: PRO60475  
 Figure 2267: DNA330181, HSM802358, 209523.at  
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 Figure 2270: DNA330182, PLAA, 209533.s.at  
 Figure 2271: PRO85430  
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 Figure 2276: DNA330184, BC022475, 209566.at  
 Figure 2277: PRO85432  
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 Figure 2283: PRO84819  
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 Figure 2287: PRO1917  
 Figure 2288: DNA270689, NP\_002042.1, 209604.s.at  
 Figure 2289: PRO59053  
 Figure 2290: DNA271823, NP\_004279.2, 209606.at  
 Figure 2291: PRO60104  
 Figure 2292A-B: DNA328670, BC001618, 209610.s.at  
 Figure 2293: PRO70011  
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 Figure 2296: DNA328599, HSNFKBS, 209636.at  
 Figure 2297: PRO84382  
 Figure 2298: DNA330186, NP\_004327.1, 209642.at  
 Figure 2299: PRO85434  
 Figure 2300A-B: DNA330187, HSM801454, 209649.at  
 Figure 2301: PRO85435  
 Figure 2302: DNA330188, NP\_004356.1, 209662.at  
 Figure 2303: PRO85436  
 Figure 2304: DNA323856, PAI-RBP1, 209669.s.at  
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 Figure 2309: PRO23299  
 Figure 2310A-B: DNA272671, HSU26710, 209682.at  
 Figure 2311: PRO60796  
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 Figure 2313: PRO85385  
 Figure 2314: DNA331519, HMMR, 209709.s.at

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 Figure 2317: PRO12087  
 Figure 2318: DNA330191, NP\_036249.1, 209715.at  
 Figure 2319: PRO85439  
 Figure 2320A-C: DNA254412, AF008915, 209717.at  
 Figure 2321: PRO49522  
 Figure 2322A-B: DNA330192, 234780.1, 209733.at  
 Figure 2323: PRO85440  
 Figure 2324: DNA330193, BC015929, 209750.at  
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 Figure 2326: PRO85442  
 Figure 2327: DNA275195, NP\_001025.1, 209773.s\_at  
 Figure 2328: PRO62893  
 Figure 2329: DNA329205, NP\_001343.1, 209782.s\_at  
 Figure 2330: PRO84821  
 Figure 2331: DNA226436, NP\_001772.1, 209795.at  
 Figure 2332: PRO36899  
 Figure 2333: DNA327731, NP\_003302.1, 209803.s\_at  
 Figure 2334: PRO83707  
 Figure 2335A-B: DNA271368, HUMKIAAI, 209804.at  
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 Figure 2338: PRO84822  
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 Figure 2344: PRO84448  
 Figure 2345A-B: DNA196499, AB002384, 209829.at  
 Figure 2346: PRO24988  
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 Figure 2348: PRO85445  
 Figure 2349: DNA328677, AF060511, 209836.x\_at  
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 Figure 2354: PRO58719  
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 Figure 2356: PRO22775  
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 Figure 2358: PRO85446  
 Figure 2359: DNA324184, NP\_065726.1, 209891.at  
 Figure 2360: PRO80882  
 Figure 2361: DNA328258, HSM802616, 209900.s\_at  
 Figure 2362: PRO84151  
 Figure 2363: DNA330152, DUT, 209932.s\_at  
 Figure 2364: PRO85406  
 Figure 2365: DNA150133, AAD01646.1, 209933.s\_at  
 Figure 2366: PRO12219  
 Figure 2367: DNA329208, CFLAR, 209939.x\_at  
 Figure 2368: PRO84823  
 Figure 2369: DNA330199, BC004357, 209944.at  
 Figure 2370: PRO85447  
 Figure 2371A-B: DNA329065, HSU12767, 209959.at  
 Figure 2372: PRO84725  
 Figure 2373: DNA154921, DNA154921, 209967.s\_at  
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 Figure 2375: PRO83711  
 Figure 2376: DNA324895, JTV1, 209971.x\_at  
 Figure 2377: PRO81501  
 Figure 2378: DNA226658, NP\_003736.1, 209999.x\_at  
 Figure 2379: PRO37121  
 Figure 2380: DNA226658, SSI-1, 210001.s\_at  
 Figure 2381: PRO37121  
 Figure 2382: DNA330200, NP\_056222.1, 210006.at  
 Figure 2383: PRO85448  
 Figure 2384: DNA269534, NP\_002155.1, 210029.at  
 Figure 2385: PRO57950  
 Figure 2386: DNA326054, NP\_002159.1, 210046.s\_at  
 Figure 2387: PRO82489  
 Figure 2388: DNA326809, NP\_036244.2, 210052.s\_at  
 Figure 2389: PRO83142  
 Figure 2390: DNA150551, AAB97010.1, 210054.at  
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 Figure 2392: DNA274960, SFRS5, 210077.s\_at  
 Figure 2393: PRO62694  
 Figure 2394: DNA324922, BC018962, 210095.s\_at  
 Figure 2395: PRO119  
 Figure 2396A-B: DNA328685, NP\_127497.1, 210113.s\_at  
 Figure 2397: PRO34751  
 Figure 2398: DNA330201, NP\_003774.1, 210121.at  
 Figure 2399: PRO50625  
 Figure 2400: DNA330202, NP\_005400.1, 210163.at  
 Figure 2401: PRO19838  
 Figure 2402: DNA287620, NP\_004122.1, 210164.at  
 Figure 2403: PRO2081  
 Figure 2404: DNA270196, HUMZFM1B, 210172.at  
 Figure 2405: PRO58584  
 Figure 2406: DNA330203, NP\_003755.1, 210190.at  
 Figure 2407: PRO85449  
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 Figure 2409: DNA331522, AF068918, 210202.s\_at  
 Figure 2410: PRO86553  
 Figure 2411: DNA331523, RAD1, 210216.x\_at  
 Figure 2412: PRO61690  
 Figure 2413: DNA328467, AF056322, 210218.s\_at  
 Figure 2414: PRO84293  
 Figure 2415: DNA217253, NP\_000749.1, 210229.s\_at  
 Figure 2416: PRO34295  
 Figure 2417: DNA331084, BC008487, 210254.at  
 Figure 2418: PRO81984  
 Figure 2419A-B: DNA270015, NP\_003444.1, 210281.s\_at  
 Figure 2420: PRO58410  
 Figure 2421: DNA330206, NP\_005801.2, 210288.at  
 Figure 2422: PRO85450

Figure 2423: DNA329945, SEC23B, 210293.s\_at  
Figure 2424: PRO85252  
Figure 2425: DNA218653, NP\_003799.1, 210314.x\_at  
Figure 2426: PRO34449  
Figure 2427: DNA326239, NP\_006752.1, 210317.s\_at  
Figure 2428: PRO39530  
Figure 2429: DNA329213, NP\_219491.1, 210321.at  
Figure 2430: PRO2313  
Figure 2431A-B: DNA329214, NP\_001087.1, 210337.s\_at  
Figure 2432: PRO84826  
Figure 2433: DNA225528, NP\_000610.1, 210354.at  
Figure 2434: PRO35991  
Figure 2435: DNA196621, HUMLY9, 210370.s\_at  
Figure 2436: DNA330207, BC001131, 210387.at  
Figure 2437: PRO85451  
Figure 2438: DNA226229, NP\_002432.1, 210410.s\_at  
Figure 2439: PRO36692  
Figure 2440A-B: DNA330208, AF164622, 210425.x\_at  
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Figure 2442: DNA329215, NP\_036224.1, 210439.at  
Figure 2443: PRO7424  
Figure 2444: DNA226394, NP\_002552.1, 210448.s\_at  
Figure 2445: PRO36857  
Figure 2446: DNA331524, BC003388, 210458.s\_at  
Figure 2447: PRO86554  
Figure 2448: DNA331525, BC002448, 210461.s\_at  
Figure 2449: PRO86555  
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Figure 2451: PRO84827  
Figure 2452: DNA227633, NP\_001156.1, 210538.s\_at  
Figure 2453: PRO38096  
Figure 2454: DNA330209, BC000585, 210542.s\_at  
Figure 2455: PRO85453  
Figure 2456: DNA331526, BC014563, 210559.s\_at  
Figure 2457: PRO58324  
Figure 2458: DNA331527, BC001602, 210563.x\_at  
Figure 2459: PRO86556  
Figure 2460: DNA331528, AF00619, 210564.x\_at  
Figure 2461: PRO86557  
Figure 2462: DNA329217, BC003406, 210571.s\_at  
Figure 2463: PRO84828  
Figure 2464: DNA330210, HSU03858, 210607.at  
Figure 2465: PRO126  
Figure 2466: DNA330211, NP\_009092.1, 210629.x\_at  
Figure 2467: PRO85454  
Figure 2468: DNA330212, HUMKRT10A, 210633.x\_at  
Figure 2469: PRO85455  
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Figure 2471: PRO86558  
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Figure 2473: PRO12135  
Figure 2474: DNA329218, NP\_055227.1, 210691.s\_at  
Figure 2475: PRO84829  
Figure 2476: DNA330215, DKFZp762A227Homo, 210692.s\_at  
Figure 2477: DNA331530, AF064103, 210742.at  
Figure 2478: PRO86559  
Figure 2479: DNA237817, NP\_001307.1, 210766.s\_at  
Figure 2480: PRO38923  
Figure 2481A-B: DNA330216, NP\_006445.1, 210778.s\_at  
Figure 2482: PRO85457  
Figure 2483: DNA226881, FLI1, 210786.s\_at  
Figure 2484: PRO37344  
Figure 2485: DNA255402, NP\_055288.1, 210802.s\_at  
Figure 2486: PRO50469  
Figure 2487: DNA330027, SSBP2, 210829.s\_at  
Figure 2488: PRO85312  
Figure 2489: DNA329219, BC000385, 210844.x\_at  
Figure 2490: PRO81278  
Figure 2491A-B: DNA331107, HSU26455, 210858.x\_at  
Figure 2492: PRO86255  
Figure 2493: DNA188234, NP\_000630.1, 210865.at  
Figure 2494: PRO21942  
Figure 2495: DNA331531, PFDN5, 210908.s\_at  
Figure 2496: PRO86560  
Figure 2497: DNA330217, AF043183, 210915.x\_at  
Figure 2498: PRO85458  
Figure 2499: DNA274326, NP\_003079.1, 210933.s\_at  
Figure 2500: PRO62244  
Figure 2501: DNA329317, NP\_057353.1, 210948.s\_at  
Figure 2502: PRO81157  
Figure 2503: DNA331532, AF125393, 210951.x\_at  
Figure 2504: PRO86561  
Figure 2505: DNA330218, HUMTCAXA, 210972.x\_at  
Figure 2506: DNA273236, NP\_004306.1, 210980.s\_at  
Figure 2507: PRO61263  
Figure 2508: DNA269888, NP\_002073.1, 210981.s\_at  
Figure 2509: PRO58286  
Figure 2510: DNA329221, HLA-DRA, 210982.s\_at  
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Figure 2512: DNA238565, MCM7, 210983.s\_at  
Figure 2513: PRO39210  
Figure 2514: DNA326239, YWHAE, 210996.s\_at  
Figure 2515: PRO39530  
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Figure 2519: PRO83682  
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Figure 2521: PRO69536  
Figure 2522: DNA329992, MGAT2, 211061.s\_at  
Figure 2523: PRO59267  
Figure 2524: DNA324171, NP\_065438.1, 211070.x\_at  
Figure 2525: PRO60753

- Figure 2526: DNA330220, NP\_006809.1, 211071.s\_at  
Figure 2527: PRO60769  
Figure 2528: DNA287198, K-ALPHA-1, 211072.x\_at  
Figure 2529: PRO69484  
Figure 2530: DNA254470, NEK2, 211080.s\_at  
Figure 2531: PRO49578  
Figure 2532: DNA196432, AF064804, 211106.at  
Figure 2533: PRO24928  
Figure 2534: DNA330202, CXCL11, 211122.s\_at  
Figure 2535: PRO19838  
Figure 2536: DNA304765, HUMTCRGAD, 211144.x\_at  
Figure 2537: PRO71178  
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Figure 2539A-B: DNA328700, SCD, 211162.x\_at  
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Figure 2542: PRO85460  
Figure 2543: DNA330222, NP\_003848.1, 211226.at  
Figure 2544: PRO45958  
Figure 2545: DNA218278, IL2RA, 211269.s\_at  
Figure 2546: PRO34330  
Figure 2547: DNA151022, DGKA, 211272.s\_at  
Figure 2548: PRO12096  
Figure 2549: DNA330223, NP\_001790.1, 211297.s\_at  
Figure 2550: PRO49730  
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Figure 2552: PRO84551  
Figure 2553: DNA188234, TNFSF6, 211333.s\_at  
Figure 2554: PRO21942  
Figure 2555: DNA103395, HSU80737, 211352.s\_at  
Figure 2556: PRO4723  
Figure 2557A-B: DNA275066, NP\_000170.1, 211450.s\_at  
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Figure 2559: DNA327755, NP\_115957.1, 211458.s\_at  
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Figure 2562: PRO4515  
Figure 2563: DNA330175, KNSL6, 211519.s\_at  
Figure 2564: PRO59681  
Figure 2565: DNA327756, NP\_068814.2, 211538.s\_at  
Figure 2566: PRO83726  
Figure 2567: DNA269888, GPRK6, 211543.s\_at  
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Figure 2582: DNA328706, BC021909, 211714.x\_at  
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Figure 2584: DNA88307, NP\_001992.1, 211734.s\_at  
Figure 2585: PRO2280  
Figure 2586: DNA329225, EVI2B, 211742.s\_at  
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Figure 2589: PRO3629  
Figure 2590: DNA328649, TUBA6, 211750.x\_at  
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Figure 2605: PRO86563  
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Figure 2622: DNA226176, CXCR4, 211919.s\_at  
Figure 2623: PRO36639  
Figure 2624: DNA272286, CAT, 211922.s\_at  
Figure 2625: PRO60544  
Figure 2626: DNA330229, BC011915, 211926.s\_at  
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Figure 2633: PRO81851

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 Figure 2648: PRO69690  
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 Figure 2652: PRO36926  
 Figure 2653A-D: DNA103461, HSMKI67, 212022.s.at  
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 Figure 2682: PRO85474

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 Figure 2689: DNA330241, AF314185, 212176.at  
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 Figure 2693: DNA330243, BC015663, 212190.at  
 Figure 2694: PRO2584  
 Figure 2695: DNA326233, RPL13, 212191.x.at  
 Figure 2696: PRO82645  
 Figure 2697A-C: DNA330244, 253946.17, 212196.at  
 Figure 2698: PRO85478  
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 Figure 2737: PRO69476

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 Figure 2754: PRO11708  
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 Figure 2794: PRO85490  
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 Figure 2834: PRO59530

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 Figure 2884: DNA106374, DNA106374, 213164.at

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 Figure 2978: PRO69493  
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 Figure 2981: DNA151041, HSAMYB2, 213906.at  
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 Figure 2983: PRO85521  
 Figure 2984: DNA330295, NP\_037515.1, 213951.s.at  
 Figure 2985: PRO85522  
 Figure 2986: DNA327807, NP\_115613.1, 213975.s.at  
 Figure 2987: PRO83768  
 Figure 2988: DNA327808, NP\_002961.1, 213988.s.at  
 Figure 2989: PRO83769  
 Figure 2990: DNA329136, HSPC111, 214011.s.at  
 Figure 2991: PRO84772  
 Figure 2992: DNA196110, DNA196110, 214016.s.at  
 Figure 2993: PRO24635  
 Figure 2994: DNA227224, LC27, 214039.s.at  
 Figure 2995: PRO37687  
 Figure 2996: DNA330296, 206955.3, 214054.at  
 Figure 2997: PRO85523  
 Figure 2998: DNA273696, DNA273696, 214060.at  
 Figure 2999A-B: DNA330297, AF378753, 214081.at  
 Figure 3000: PRO85524  
 Figure 3001: DNA227091, NP\_000256.1, 214084.x.at  
 Figure 3002: PRO37554  
 Figure 3003: DNA331557, BC016778, 214085.x.at  
 Figure 3004: PRO86576  
 Figure 3005: DNA254686, NP\_005475.1, 214086.s.at  
 Figure 3006: PRO49786  
 Figure 3007: DNA330298, BC011911, 214095.at  
 Figure 3008: PRO83772  
 Figure 3009: DNA329254, BC004215, 214096.s.at  
 Figure 3010: PRO84854  
 Figure 3011: DNA330299, AK023737, 214102.at  
 Figure 3012: PRO85525  
 Figure 3013: DNA331360, AK022497, 214177.s.at  
 Figure 3014: PRO86435  
 Figure 3015A-B: DNA269826, NP\_003195.1, 214179.s.at  
 Figure 3016: PRO58228  
 Figure 3017: DNA331558, AF000424, 214181.x.at  
 Figure 3018: PRO86577  
 Figure 3019: DNA290295, NP\_055203.1, 214193.s.at  
 Figure 3020: PRO70455  
 Figure 3021: DNA327701, C1QBP, 214214.s.at  
 Figure 3022: PRO82667  
 Figure 3023: DNA331361, NP\_003318.1, 214228.x.at  
 Figure 3024: PRO2398  
 Figure 3025: DNA154914, DNA154914, 214230.at  
 Figure 3026: DNA330300, NP\_004883.1, 214257.s.at  
 Figure 3027: PRO41086  
 Figure 3028: DNA273940, DNA273940, 214272.at  
 Figure 3029: DNA97279, JUND, 214326.x.at  
 Figure 3030: PRO3628  
 Figure 3031: DNA84130, HSU37518, 214329.x.at  
 Figure 3032: PRO1096  
 Figure 3033: DNA272928, DAZAP2, 214334.x.at  
 Figure 3034: PRO61012  
 Figure 3035: DNA331362, AF275719, 214359.s.at  
 Figure 3036: PRO86436  
 Figure 3037: DNA331559, AF043723, 214368.at  
 Figure 3038: PRO85114  
 Figure 3039: DNA328611, AF043722, 214369.s.at  
 Figure 3040: PRO84393

- Figure 3041: DNA273138, NP\_005495.1, 214390.s\_at  
 Figure 3042: PRO61182  
 Figure 3043: DNA273174, NP\_001951.1, 214394.x\_at  
 Figure 3044: PRO61211  
 Figure 3045: DNA328782, 337794.1, 214405.at  
 Figure 3046: PRO84528  
 Figure 3047: DNA326090, NP\_000549.1, 214414.x\_at  
 Figure 3048: PRO3629  
 Figure 3049: DNA271374, CHAF1A, 214426.x\_at  
 Figure 3050: PRO59673  
 Figure 3051: DNA287630, NP\_000160.1, 214430.at  
 Figure 3052: PRO2154  
 Figure 3053: DNA327811, SHMT2, 214437.s\_at  
 Figure 3054: PRO83772  
 Figure 3055: DNA331363, AF001383, 214439.x\_at  
 Figure 3056: PRO86437  
 Figure 3057: DNA331560, NP\_001326.1, 214450.at  
 Figure 3058: PRO85081  
 Figure 3059: DNA273138, BCAT1, 214452.at  
 Figure 3060: PRO61182  
 Figure 3061: DNA327812, NP\_006408.2, 214453.s\_at  
 Figure 3062: PRO83773  
 Figure 3063: DNA150971, NP\_002249.1, 214470.at  
 Figure 3064: PRO12564  
 Figure 3065: DNA330301, NP\_008908.1, 214482.at  
 Figure 3066: PRO85526  
 Figure 3067: DNA325246, RRP4, 214507.s\_at  
 Figure 3068: PRO81800  
 Figure 3069: DNA331561, CREM, 214508.x\_at  
 Figure 3070: PRO86578  
 Figure 3071: DNA331562, NP\_003090.1, 214531.s\_at  
 Figure 3072: PRO58654  
 Figure 3073: DNA216515, NP\_003166.1, 214567.s\_at  
 Figure 3074: PRO34267  
 Figure 3075: DNA331223, HUMPRF1M, 214617.at  
 Figure 3076: DNA331563, BC004101, 214643.x\_at  
 Figure 3077: PRO86579  
 Figure 3078: DNA150552, AAB97011.1, 214661.s\_at  
 Figure 3079: PRO12326  
 Figure 3080: DNA330303, BAA05499.1, 214662.at  
 Figure 3081: PRO85528  
 Figure 3082: DNA330304, HSIGVL026, 214677.x\_at  
 Figure 3083: PRO85529  
 Figure 3084: DNA287355, ALDOA, 214687.x\_at  
 Figure 3085: PRO69617  
 Figure 3086: DNA330305, HSU79263, 214700.x\_at  
 Figure 3087: DNA288259, NP\_114172.1, 214710.s\_at  
 Figure 3088: PRO4676  
 Figure 3089: DNA324984, NP\_115540.1, 214714.at  
 Figure 3090: PRO81578  
 Figure 3091: DNA330306, 407311.1, 214743.at  
 Figure 3092: PRO85531  
 Figure 3093: DNA331564, BC014654, 214752.x\_at  
 Figure 3094: PRO86580  
 Figure 3095: DNA254338, AAA60119.1, 214765.s\_at  
 Figure 3096: PRO49449  
 Figure 3097: DNA275473, DNA275473, 214787.at  
 Figure 3098A-B: DNA272353, AB007958, 214833.at  
 Figure 3099: DNA226577, C6orf9, 214847.s\_at  
 Figure 3100: PRO37040  
 Figure 3101A-B: DNA331565, BAA34472.1, 214945.at  
 Figure 3102: PRO86581  
 Figure 3103: DNA328530, LAK-4P, 214958.s\_at  
 Figure 3104: PRO24118  
 Figure 3105A-B: DNA271654, AB020704, 214978.s\_at  
 Figure 3106A-B: DNA329261, HSM802517, 215001.s\_at  
 Figure 3107: PRO84859  
 Figure 3108: DNA330308, 307914.1, 215029.at  
 Figure 3109: PRO85533  
 Figure 3110: DNA196372, HSBCLXL, 215037.s\_at  
 Figure 3111: PRO24874  
 Figure 3112: DNA331566, AIF1, 215051.x\_at  
 Figure 3113: PRO86582  
 Figure 3114: DNA330309, NP\_003503.1, 215071.s\_at  
 Figure 3115: PRO85534  
 Figure 3116A-B: DNA330307, AB018295, 215133.s\_at  
 Figure 3117: DNA331567, 333089.1, 215147.at  
 Figure 3118: PRO86583  
 Figure 3119: DNA273371, UMPS, 215165.x\_at  
 Figure 3120: PRO61373  
 Figure 3121A-B: DNA150496, AB023212, 215175.at  
 Figure 3122A-B: DNA220748, ITGA6, 215177.s\_at  
 Figure 3123: PRO34726  
 Figure 3124: DNA330311, 405318.1, 215221.at  
 Figure 3125: PRO85536  
 Figure 3126: DNA227597, NP\_000627.1, 215223.s\_at  
 Figure 3127: PRO38060  
 Figure 3128A-B: DNA330312, 406407.1, 215262.at  
 Figure 3129: PRO85537  
 Figure 3130: DNA331568, TADA3L, 215273.s\_at  
 Figure 3131: PRO80953  
 Figure 3132: DNA330314, 026641.5, 215275.at  
 Figure 3133: PRO85538  
 Figure 3134: DNA330315, 1500205.1, 215283.at  
 Figure 3135: PRO85539  
 Figure 3136: DNA330316, 1448781.1, 215284.at  
 Figure 3137: PRO85540  
 Figure 3138: DNA330317, 228133.1, 215330.at  
 Figure 3139: PRO85541  
 Figure 3140: DNA331569, NP\_000552.1, 215333.x\_at  
 Figure 3141: PRO85542  
 Figure 3142: DNA327831, NP\_076956.1, 215380.s\_at  
 Figure 3143: PRO83783  
 Figure 3144: DNA328801, 407831.1, 215392.at  
 Figure 3145: PRO84543  
 Figure 3146: DNA325174, NP\_038470.1, 215416.s\_at  
 Figure 3147: PRO9819  
 Figure 3148: DNA275385, NP\_002085.1, 215438.x\_at

- Figure 3149: PRO63048  
Figure 3150: DNA331570, BC015794, 215440.s\_at  
Figure 3151: PRO84545  
Figure 3152: DNA330319, AF247727, 215483\_at  
Figure 3153: DNA331571, MAP2K3, 215498.s\_at  
Figure 3154: PRO86584  
Figure 3155: DNA330186, BUB1, 215509.s\_at  
Figure 3156: PRO85434  
Figure 3157: DNA330321, 315726.1, 215605\_at  
Figure 3158: PRO85545  
Figure 3159: DNA331572, AF000426, 215633.x\_at  
Figure 3160: PRO86585  
Figure 3161: DNA330031, LOC51668, 215691.x\_at  
Figure 3162: PRO85316  
Figure 3163: DNA331573, HSAPT1, 215719.x\_at  
Figure 3164A-B: DNA254376, KIAA0963, 215760.s\_at  
Figure 3165: PRO49486  
Figure 3166A-B: DNA328805, BAA86482.1, 215785.s\_at  
Figure 3167: PRO84547  
Figure 3168: DNA331574, HUMTCGCH, 215806.x\_at  
Figure 3169: DNA330322, 234025.21, 215855.s\_at  
Figure 3170: PRO85546  
Figure 3171: DNA330323, 335053.1, 215908\_at  
Figure 3172: PRO85547  
Figure 3173: DNA330324, HHEX, 215933.s\_at  
Figure 3174: PRO58034  
Figure 3175: DNA331575, AF223408, 215942.s\_at  
Figure 3176: PRO86587  
Figure 3177: DNA330325, NP\_055057.1, 215948.x\_at  
Figure 3178: PRO85548  
Figure 3179: DNA227668, GK, 215966.x\_at  
Figure 3180: PRO38131  
Figure 3181: DNA330326, AY007142, 215967.s\_at  
Figure 3182: PRO85549  
Figure 3183: DNA331576, HSRNAGLK, 215977.x\_at  
Figure 3184: DNA188736, U00115, 215990.s\_at  
Figure 3185: PRO26296  
Figure 3186: DNA331577, 208045.1, 216109\_at  
Figure 3187: PRO86588  
Figure 3188: DNA331578, HSTCELD, 216133\_at  
Figure 3189: PRO86589  
Figure 3190: DNA254783, DKC1, 216212.s\_at  
Figure 3191: PRO49881  
Figure 3192A-B: DNA255273, AB029015, 216218.s\_at  
Figure 3193A-B: DNA256461, AND-1, 216228.s\_at  
Figure 3194: PRO51498  
Figure 3195: DNA329266, BC000142, 216237.s\_at  
Figure 3196: PRO12845  
Figure 3197: DNA151048, HSNOT, 216248.s\_at  
Figure 3198: PRO12850  
Figure 3199: DNA329155, BC012479, 216252.x\_at  
Figure 3200: PRO1207  
Figure 3201: DNA331579, HSCLCA, 216295.s\_at  
Figure 3202: DNA88189, CD24, 216379.x\_at  
Figure 3203: PRO2690  
Figure 3204: DNA330329, IR1875335, 216483.s\_at  
Figure 3205: DNA287243, NP\_004452.1, 216602.s\_at  
Figure 3206: PRO69518  
Figure 3207: DNA331580, 1099517.2, 216607.s\_at  
Figure 3208: PRO86590  
Figure 3209: DNA227874, TXN, 216609\_at  
Figure 3210: PRO38337  
Figure 3211: DNA88296, NP\_005733.1, 216640.s\_at  
Figure 3212: PRO2274  
Figure 3213: DNA269692, S59049, 216834\_at  
Figure 3214: PRO58102  
Figure 3215: DNA227597, SOD2, 216841.s\_at  
Figure 3216: PRO38060  
Figure 3217A-B: DNA330331, BAA86451.1, 216873.s\_at  
Figure 3218: PRO85554  
Figure 3219: DNA188275, NP\_002181.1, 216876.s\_at  
Figure 3220: PRO21800  
Figure 3221A-B: DNA150987, NP\_006051.1, 216901.s\_at  
Figure 3222: PRO12163  
Figure 3223: DNA329267, HUMTCRGAAC, 216920.s\_at  
Figure 3224A-C: DNA328811, HUMINSP3R1, 216944.s\_at  
Figure 3225: PRO84551  
Figure 3226A-B: DNA151027, AAA80979.1, 216952.s\_at  
Figure 3227: PRO12843  
Figure 3228A-E: DNA269650, PLEC1, 216971.s\_at  
Figure 3229A-B: PRO58061  
Figure 3230: DNA328812, BAA86575.1, 216997.x\_at  
Figure 3231: PRO84552  
Figure 3232: DNA331581, AAB59396.1, 217022.s\_at  
Figure 3233: PRO86591  
Figure 3234: DNA331366, HUMGPCR, 217028\_at  
Figure 3235: PRO4516  
Figure 3236A-B: DNA227293, AB020721, 217047.s\_at  
Figure 3237: PRO37756  
Figure 3238A-B: DNA329269, BAA32292.2, 217122.s\_at  
Figure 3239: PRO84865  
Figure 3240: DNA331582, AAA59588.1, 217165.x\_at  
Figure 3241: PRO86592  
Figure 3242: DNA331583, S70123, 217173.s\_at  
Figure 3243: DNA331584, AF105973, 217232.x\_at  
Figure 3244: PRO86593  
Figure 3245: DNA330334, NP\_114402.1, 217286.s\_at  
Figure 3246: PRO85557  
Figure 3247: DNA331369, HSU88968, 217294.s\_at  
Figure 3248A-B: DNA331585, AF051334, 217299.s\_at  
Figure 3249: PRO86594

Figure 3250: DNA331586, S81916, 217356.s\_at  
 Figure 3251: DNA331587, HSNGMRNA, 217398.x\_at  
 Figure 3252: PRO86595  
 Figure 3253: DNA330335, NP\_054765.1, 217408.at  
 Figure 3254: PRO62166  
 Figure 3255: DNA331588, AF097635, 217414.x\_at  
 Figure 3256: PRO3629  
 Figure 3257: DNA329539, HLA-DMA, 217478.s\_at  
 Figure 3258: PRO85089  
 Figure 3259: DNA331589, 243999.2, 217502.at  
 Figure 3260: PRO86596  
 Figure 3261: DNA329271, 406848.1, 217591.at  
 Figure 3262: PRO84867  
 Figure 3263: DNA330337, 1447003.1, 217616.at  
 Figure 3264: PRO85559  
 Figure 3265: DNA331590, 368556.1, 217655.at  
 Figure 3266: PRO86597  
 Figure 3267: DNA330339, HSA012375, 217672.x\_at  
 Figure 3268: DNA323856, HSM800628, 217725.x\_at  
 Figure 3269: PRO80599  
 Figure 3270: DNA326523, NP\_001121.2, 217729.s\_at  
 Figure 3271: PRO71126  
 Figure 3272: DNA325832, NP\_068839.1, 217731.s\_at  
 Figure 3273: PRO1869  
 Figure 3274A-B: DNA327847, 142131.14, 217738.at  
 Figure 3275: PRO2834  
 Figure 3276: DNA88541, NP\_005737.1, 217739.s\_at  
 Figure 3277: PRO2834  
 Figure 3278: DNA327935, NP\_079422.1, 217745.s\_at  
 Figure 3279: PRO83866  
 Figure 3280: DNA327849, NP\_057269.1, 217755.at  
 Figure 3281: PRO83794  
 Figure 3282A-B: DNA274131, AF183421, 217762.s\_at  
 Figure 3283: PRO62067  
 Figure 3284: DNA330340, NP\_006859.1, 217763.s\_at  
 Figure 3285: PRO85562  
 Figure 3286A-B: DNA274131, DNA274131, 217764.s\_at  
 Figure 3287: PRO62067  
 Figure 3288: DNA325821, NP\_057016.1, 217769.s\_at  
 Figure 3289: PRO82287  
 Figure 3290: DNA325910, AF167438, 217776.at  
 Figure 3291: PRO82365  
 Figure 3292: DNA227358, NP\_057479.1, 217777.s\_at  
 Figure 3293: PRO37821  
 Figure 3294: DNA328819, NP\_057145.1, 217783.s\_at  
 Figure 3295: PRO84557  
 Figure 3296: DNA325873, SKB1, 217786.at  
 Figure 3297: PRO82331  
 Figure 3298: DNA331591, NP\_055241.1, 217792.at  
 Figure 3299: PRO69560  
 Figure 3300: DNA328303, NP\_056525.1, 217807.s\_at  
 Figure 3301: PRO84173  
 Figure 3302: DNA227223, NP\_064583.1, 217814.at  
 Figure 3303: PRO37686  
 Figure 3304: DNA327851, NSAP1, 217834.s\_at  
 Figure 3305: PRO83795  
 Figure 3306: DNA328823, NP\_057421.1, 217838.s\_at  
 Figure 3307: PRO84561  
 Figure 3308: DNA330341, NP\_006061.2, 217839.at  
 Figure 3309: PRO85563  
 Figure 3310: DNA254773, NP\_057231.1, 217841.s\_at  
 Figure 3311: PRO49871  
 Figure 3312: DNA330342, NP\_067021.1, 217844.at  
 Figure 3313: PRO85564  
 Figure 3314: DNA329272, NP\_055181.1, 217850.at  
 Figure 3315: PRO84868  
 Figure 3316A-B: DNA330343, AF403012, 217857.s\_at  
 Figure 3317: DNA330344, NP\_057392.1, 217870.s\_at  
 Figure 3318: PRO85565  
 Figure 3319: DNA326937, NP\_002406.1, 217871.s\_at  
 Figure 3320: PRO83255  
 Figure 3321: DNA330345, NP\_055130.1, 217906.at  
 Figure 3322: PRO85566  
 Figure 3323: DNA330346, NP\_054880.2, 217907.at  
 Figure 3324: PRO85567  
 Figure 3325: DNA325780, NP\_060371.1, 217914.at  
 Figure 3326: PRO82250  
 Figure 3327: DNA327853, NP\_054769.1, 217919.s\_at  
 Figure 3328: PRO82223  
 Figure 3329: DNA330347, 255559.4, 217922.at  
 Figure 3330: PRO85568  
 Figure 3331: DNA330348, NP\_079150.1, 217929.s\_at  
 Figure 3332: PRO85569  
 Figure 3333: DNA330349, BC022093, 217931.at  
 Figure 3334: DNA287241, NP\_056991.1, 217933.s\_at  
 Figure 3335: PRO69516  
 Figure 3336A-B: DNA225648, NP\_061165.1, 217941.s\_at  
 Figure 3337: PRO36111  
 Figure 3338: DNA326730, NP\_057037.1, 217950.at  
 Figure 3339: PRO83072  
 Figure 3340: DNA329273, NP\_037374.1, 217957.at  
 Figure 3341: PRO84869  
 Figure 3342: DNA328829, NP\_057230.1, 217959.s\_at  
 Figure 3343: PRO84566  
 Figure 3344: DNA328830, NP\_061118.1, 217962.at  
 Figure 3345: PRO84567  
 Figure 3346: DNA329274, NP\_055195.1, 217963.s\_at  
 Figure 3347: PRO84870  
 Figure 3348: DNA325496, NP\_037397.2, 217969.at  
 Figure 3349: PRO82013  
 Figure 3350: DNA327855, NP\_057387.1, 217975.at  
 Figure 3351: PRO83367  
 Figure 3352: DNA227218, NP\_003721.2, 217983.s\_at  
 Figure 3353: PRO37681  
 Figure 3354: DNA227218, RNASE6PL, 217984.at  
 Figure 3355: PRO37681  
 Figure 3356A-B: DNA227238, NP\_038476.1, 217985.s\_at

Figure 3357: PRO37701  
Figure 3358A-B: DNA227238, BAZ1A, 217986.s.at  
Figure 3359: PRO37701  
Figure 3360: DNA328831, NP\_057329.1, 217989.at  
Figure 3361: PRO233  
Figure 3362: DNA328832, NP\_067022.1, 217995.at  
Figure 3363: PRO84568  
Figure 3364: DNA328833, BC018929, 217996.at  
Figure 3365: PRO84569  
Figure 3366: DNA328834, AF220656, 217997.at  
Figure 3367: DNA287364, NP\_031376.1, 218000.s.at  
Figure 3368: PRO69625  
Figure 3369: DNA273008, NP\_003972.1, 218009.s.at  
Figure 3370: PRO61079  
Figure 3371: DNA330350, NP\_006108.1, 218025.s.at  
Figure 3372: PRO85570  
Figure 3373: DNA328836, NP\_054894.1, 218027.at  
Figure 3374: PRO84572  
Figure 3375: DNA329275, AF070673, 218032.at  
Figure 3376: PRO12342  
Figure 3377: DNA331592, ANKT, 218039.at  
Figure 3378: PRO82424  
Figure 3379: DNA328838, NP\_054797.2, 218049.s.at  
Figure 3380: PRO70319  
Figure 3381: DNA330352, NP\_075059.1, 218051.s.at  
Figure 3382: PRO85571  
Figure 3383: DNA329276, NP\_077001.1, 218069.at  
Figure 3384: PRO12104  
Figure 3385: DNA328841, NP\_060557.2, 218073.s.at  
Figure 3386: PRO84575  
Figure 3387: DNA329277, NP\_054883.3, 218084.x.at  
Figure 3388: PRO6241  
Figure 3389: DNA330353, BC020796, 218085.at  
Figure 3390: PRO69464  
Figure 3391: DNA329278, NP\_004495.1, 218092.s.at  
Figure 3392: PRO84871  
Figure 3393: DNA227313, NP\_060945.1, 218095.s.at  
Figure 3394: PRO37776  
Figure 3395: DNA331593, MRPL4, 218105.s.at  
Figure 3396: PRO86598  
Figure 3397: DNA326596, NP\_060624.1, 218115.at  
Figure 3398: PRO82954  
Figure 3399: DNA330355, NP\_055063.1, 218117.at  
Figure 3400: PRO83289  
Figure 3401: DNA330356, NP\_006318.1, 218118.s.at  
Figure 3402: PRO85572  
Figure 3403: DNA330357, NP\_078786.2, 218130.at  
Figure 3404: PRO85573  
Figure 3405: DNA227155, NP\_057654.1, 218135.at  
Figure 3406: PRO37618  
Figure 3407: DNA254496, NP\_060076.1, 218149.s.at  
Figure 3408: PRO49604  
Figure 3409: DNA330358, NP\_079012.1, 218154.at  
Figure 3410: PRO85574  
Figure 3411: DNA254739, NP\_068766.1, 218156.s.at  
Figure 3412: PRO49837

Figure 3413: DNA304470, PRO2577, 218172.s.at  
Figure 3414: PRO2577  
Figure 3415: DNA330359, NP\_065145.1, 218178.s.at  
Figure 3416: PRO85575  
Figure 3417: DNA304495, NP\_057156.1, 218193.s.at  
Figure 3418: PRO793  
Figure 3419A-C: DNA330360, NP\_078789.1, 218204.s.at  
Figure 3420: PRO85576  
Figure 3421: DNA327858, NP\_036473.1, 218238.at  
Figure 3422: PRO83800  
Figure 3423: DNA327858, CRFG, 218239.s.at  
Figure 3424: PRO83800  
Figure 3425A-B: DNA330361, CKAP2, 218252.at  
Figure 3426: PRO85577  
Figure 3427: DNA328850, NP\_057187.1, 218254.s.at  
Figure 3428: PRO84581  
Figure 3429: DNA331594, MRPL24, 218270.at  
Figure 3430: PRO11652  
Figure 3431: DNA273230, NP\_060914.1, 218273.s.at  
Figure 3432: PRO61257  
Figure 3433: DNA324444, NP\_006333.1, 218308.at  
Figure 3434: PRO81108  
Figure 3435: DNA330363, NP\_060252.1, 218331.s.at  
Figure 3436: PRO85578  
Figure 3437: DNA329281, NP\_036526.2, 218336.at  
Figure 3438: PRO84874  
Figure 3439A-B: DNA330364, NP\_004417.1, 218338.at  
Figure 3440: PRO85579  
Figure 3441: DNA272918, NP\_055269.1, 218346.s.at  
Figure 3442: PRO61003  
Figure 3443: DNA327862, NP\_060445.1, 218349.s.at  
Figure 3444: PRO83803  
Figure 3445: DNA328854, NP\_056979.1, 218350.s.at  
Figure 3446: PRO84585  
Figure 3447A-B: DNA273415, KIF4A, 218355.at  
Figure 3448: PRO61414  
Figure 3449: DNA324890, NP\_037525.1, 218356.at  
Figure 3450: PRO81496  
Figure 3451: DNA330365, NP\_036591.1, 218357.s.at  
Figure 3452: PRO85580  
Figure 3453A-B: DNA331595, NP\_073602.2, 218376.s.at  
Figure 3454: PRO86599  
Figure 3455: DNA330367, NP\_057174.1, 218379.at  
Figure 3456: PRO85582  
Figure 3457: DNA328856, NP\_068376.1, 218380.at  
Figure 3458: PRO84586  
Figure 3459: DNA227248, NP\_006287.1, 218397.at  
Figure 3460: PRO37711  
Figure 3461A-B: DNA287192, NP\_006178.1, 218400.at  
Figure 3462: PRO69478  
Figure 3463: DNA329912, TTC4, 218442.at  
Figure 3464: PRO85227

Figure 3465: DNA150661, NP\_057162.1, 218446.s.at  
 Figure 3466: PRO12398  
 Figure 3467: DNA304781, NP\_057385.2, 218461.at  
 Figure 3468: PRO71191  
 Figure 3469: DNA328861, NP\_057030.2, 218472.s.at  
 Figure 3470: PRO84589  
 Figure 3471: DNA330368, NP\_064446.1, 218494.s.at  
 Figure 3472: PRO85583  
 Figure 3473: DNA150648, NP\_037464.1, 218507.at  
 Figure 3474: PRO11576  
 Figure 3475: DNA328864, NP\_060726.2, 218512.at  
 Figure 3476: PRO84592  
 Figure 3477: DNA330369, NP\_060822.1, 218513.at  
 Figure 3478: PRO85584  
 Figure 3479: DNA330370, NP\_060415.1, 218519.at  
 Figure 3480: PRO190  
 Figure 3481: DNA327867, NP\_061873.2, 218532.s.at  
 Figure 3482: PRO83808  
 Figure 3483: DNA330371, NP\_060813.1, 218535.s.at  
 Figure 3484: PRO85585  
 Figure 3485: DNA327868, NP\_060601.2, 218542.at  
 Figure 3486: PRO83809  
 Figure 3487: DNA255113, NP\_073587.1, 218543.s.at  
 Figure 3488: PRO50195  
 Figure 3489: DNA330372, NP\_057117.1, 218549.s.at  
 Figure 3490: PRO85586  
 Figure 3491: DNA330373, NP\_060751.1, 218552.at  
 Figure 3492: PRO85587  
 Figure 3493: DNA330374, NP\_054901.1, 218556.at  
 Figure 3494: PRO23321  
 Figure 3495: DNA330375, NP\_059142.1, 218558.s.at  
 Figure 3496: PRO85588  
 Figure 3497: DNA329587, NP\_036256.1, 218566.s.at  
 Figure 3498: PRO85121  
 Figure 3499: DNA329286, NP\_005691.2, 218567.x.at  
 Figure 3500: PRO69644  
 Figure 3501: DNA329054, NP\_078805.2, 218578.at  
 Figure 3502: PRO84716  
 Figure 3503A-B: DNA273435, NP\_057532.1, 218585.s.at  
 Figure 3504: PRO61430  
 Figure 3505: DNA227327, NP\_060547.1, 218593.at  
 Figure 3506: PRO37790  
 Figure 3507: DNA328628, NP\_060542.2, 218594.at  
 Figure 3508: PRO84406  
 Figure 3509: DNA287642, NP\_060934.1, 218597.s.at  
 Figure 3510: PRO9902  
 Figure 3511A-B: DNA254789, NP\_057301.1, 218603.at  
 Figure 3512: PRO49887  
 Figure 3513: DNA330376, NP\_076962.1, 218622.at  
 Figure 3514: PRO85589  
 Figure 3515: DNA327869, NP\_057672.1, 218625.at  
 Figure 3516: PRO1898  
 Figure 3517: DNA330377, NP\_036577.1, 218638.s.at  
 Figure 3518: PRO85590  
 Figure 3519: DNA330378, NP\_071741.2, 218662.s.at  
 Figure 3520: PRO81126  
 Figure 3521: DNA330378, HCAP-G, 218663.at  
 Figure 3522: PRO81126  
 Figure 3523: DNA287291, NP\_067036.1, 218676.s.at  
 Figure 3524: PRO69561  
 Figure 3525: DNA304835, NP\_071327.1, 218681.s.at  
 Figure 3526: PRO71242  
 Figure 3527: DNA330379, NP\_073562.1, 218689.at  
 Figure 3528: PRO85591  
 Figure 3529: DNA329288, NP\_061910.1, 218695.at  
 Figure 3530: PRO84880  
 Figure 3531: DNA287378, NP\_060898.1, 218715.at  
 Figure 3532: PRO69637  
 Figure 3533: DNA327202, NP\_057289.1, 218718.at  
 Figure 3534: PRO200  
 Figure 3535: DNA330380, NP\_078937.2, 218722.s.at  
 Figure 3536: PRO85592  
 Figure 3537: DNA324251, NP\_060880.2, 218726.at  
 Figure 3538: PRO80935  
 Figure 3539: DNA227617, NP\_057161.1, 218732.at  
 Figure 3540: PRO38080  
 Figure 3541: DNA330381, NP\_076958.1, 218741.at  
 Figure 3542: PRO38668  
 Figure 3543: DNA330382, NP\_005724.1, 218755.at  
 Figure 3544: PRO61907  
 Figure 3545: DNA330383, NP\_054828.1, 218782.s.at  
 Figure 3546: PRO85593  
 Figure 3547: DNA330384, NP\_060388.1, 218802.at  
 Figure 3548: PRO51129  
 Figure 3549: DNA88315, NP\_004098.1, 218831.s.at  
 Figure 3550: PRO2743  
 Figure 3551: DNA330385, NP\_057733.2, 218859.s.at  
 Figure 3552: PRO85594  
 Figure 3553: DNA330386, NP\_057394.1, 218866.s.at  
 Figure 3554: PRO85595  
 Figure 3555: DNA330387, NP\_036309.1, 218875.s.at  
 Figure 3556: PRO85596  
 Figure 3557: DNA327874, BC022791, 218880.at  
 Figure 3558: PRO4805  
 Figure 3559A-B: DNA271829, NP\_006775.1, 218882.s.at  
 Figure 3560: PRO60109  
 Figure 3561: DNA330388, NP\_078905.1, 218883.s.at  
 Figure 3562: PRO85597  
 Figure 3563: DNA226633, NP\_060376.1, 218886.at  
 Figure 3564: PRO37096  
 Figure 3565: DNA304780, NP\_060562.2, 218888.s.at  
 Figure 3566: PRO69889  
 Figure 3567: DNA256762, AK022882, 218889.at  
 Figure 3568: PRO51695  
 Figure 3569: DNA328881, NP\_057706.2, 218890.x.at  
 Figure 3570: PRO49469  
 Figure 3571: DNA325622, NP\_060518.1, 218894.s.at  
 Figure 3572: PRO82113  
 Figure 3573: DNA225694, NP\_060087.1, 218902.at

Figure 3574: PRO36157  
 Figure 3575: DNA325690, NP\_076973.1, 218903.s.at  
 Figure 3576: PRO82179  
 Figure 3577: DNA328364, SIGIRR, 218921.at  
 Figure 3578: PRO84223  
 Figure 3579: DNA287166, NP\_055129.1, 218943.s.at  
 Figure 3580: PRO69459  
 Figure 3581: DNA330389, NP\_079221.1, 218979.at  
 Figure 3582: PRO85598  
 Figure 3583: DNA329050, NP\_057053.1, 218982.s.at  
 Figure 3584: PRO84712  
 Figure 3585: DNA330390, NP\_057630.1, 218983.at  
 Figure 3586: PRO85599  
 Figure 3587: DNA288277, NP\_061915.1, 218984.at  
 Figure 3588: PRO70034  
 Figure 3589: DNA256265, NP\_060101.1, 218986.s.at  
 Figure 3590: PRO51309  
 Figure 3591: DNA227194, FLJ11000, 218999.at  
 Figure 3592: PRO37657  
 Figure 3593: DNA330391, NP\_076999.1, 219000.s.at  
 Figure 3594: PRO34008  
 Figure 3595: DNA330392, NP\_078923.2, 219007.at  
 Figure 3596: PRO85600  
 Figure 3597: DNA328885, NP\_061108.2, 219017.at  
 Figure 3598: PRO50294  
 Figure 3599: DNA330393, NP\_067635.1, 219024.at  
 Figure 3600: PRO85601  
 Figure 3601: DNA329292, NP\_057185.1, 219031.s.at  
 Figure 3602: PRO84882  
 Figure 3603: DNA330394, NP\_079402.1, 219035.s.at  
 Figure 3604: PRO85602  
 Figure 3605: DNA329293, NP\_057136.1, 219037.at  
 Figure 3606: PRO84883  
 Figure 3607: DNA328886, NP\_078811.1, 219040.at  
 Figure 3608: PRO84610  
 Figure 3609: DNA331596, NP\_060841.1, 219049.at  
 Figure 3610: PRO84884  
 Figure 3611: DNA330395, NP\_060212.1, 219062.s.at  
 Figure 3612: PRO85603  
 Figure 3613: DNA330396, NP\_077303.1, 219088.s.at  
 Figure 3614: PRO85604  
 Figure 3615: DNA330397, NP\_054873.1, 219094.at  
 Figure 3616: PRO85605  
 Figure 3617: DNA331597, PLA2G4B, 219095.at  
 Figure 3618: PRO86600  
 Figure 3619: DNA330398, NP\_060367.1, 219133.at  
 Figure 3620: PRO85606  
 Figure 3621: DNA297191, NP\_060962.2, 219148.at  
 Figure 3622: PRO70808  
 Figure 3623: DNA329295, NP\_036549.1, 219155.at  
 Figure 3624: PRO84885  
 Figure 3625A-B: DNA329438, NP\_476516.1, 219158.s.at  
 Figure 3626: PRO85008  
 Figure 3627: DNA328892, NP\_067643.2, 219165.at  
 Figure 3628: PRO84616

Figure 3629: DNA330399, NP\_060609.1, 219166.at  
 Figure 3630: PRO85607  
 Figure 3631: DNA330400, NP\_078796.1, 219176.at  
 Figure 3632: PRO85608  
 Figure 3633: DNA271455, NP\_057735.1, 219179.at  
 Figure 3634: PRO59751  
 Figure 3635: DNA330401, NP\_057377.1, 219191.s.at  
 Figure 3636: PRO85609  
 Figure 3637: DNA330402, NP\_076996.1, 219200.at  
 Figure 3638: PRO85610  
 Figure 3639: DNA287235, NP\_060598.1, 219204.s.at  
 Figure 3640: PRO69514  
 Figure 3641: DNA327879, NP\_071451.1, 219209.at  
 Figure 3642: PRO83818  
 Figure 3643: DNA330403, NP\_059110.1, 219211.at  
 Figure 3644: PRO85611  
 Figure 3645: DNA330404, ZNF361, 219228.at  
 Figure 3646: PRO85612  
 Figure 3647: DNA225594, NP\_037404.1, 219229.at  
 Figure 3648: PRO36057  
 Figure 3649: DNA328894, NP\_060796.1, 219243.at  
 Figure 3650: PRO84617  
 Figure 3651: DNA329296, NP\_060328.1, 219258.at  
 Figure 3652: PRO84886  
 Figure 3653: DNA304461, NP\_054877.1, 219283.at  
 Figure 3654: PRO71039  
 Figure 3655: DNA330405, RBM15, 219286.s.at  
 Figure 3656: PRO85613  
 Figure 3657A-B: DNA329076, NP\_064627.1, 219306.at  
 Figure 3658: PRO84733  
 Figure 3659: DNA329914, FLJ12542, 219311.at  
 Figure 3660: PRO85229  
 Figure 3661: DNA255939, NP\_078876.1, 219315.s.at  
 Figure 3662: PRO50991  
 Figure 3663: DNA287404, NP\_073748.1, 219334.s.at  
 Figure 3664: PRO69661  
 Figure 3665: DNA254710, NP\_060382.1, 219352.at  
 Figure 3666: PRO49810  
 Figure 3667: DNA325169, HSPC177, 219356.s.at  
 Figure 3668: PRO81734  
 Figure 3669: DNA330406, NP\_079368.1, 219359.at  
 Figure 3670: PRO85614  
 Figure 3671: DNA330407, NP\_057026.2, 219363.s.at  
 Figure 3672: PRO85615  
 Figure 3673: DNA330408, NP\_077024.1, 219364.at  
 Figure 3674: PRO85616  
 Figure 3675: DNA254518, NP\_057354.1, 219371.s.at  
 Figure 3676: PRO49625  
 Figure 3677: DNA327886, NP\_060832.1, 219399.at  
 Figure 3678: PRO41077  
 Figure 3679: DNA256417, NP\_077271.1, 219402.s.at  
 Figure 3680: PRO51457  
 Figure 3681A-B: DNA327887, NP\_006656.1, 219403.s.at  
 Figure 3682: PRO83823

Figure 3683: DNA271811, NP\_036514.1, 219421.at  
 Figure 3684: PRO60092  
 Figure 3685: DNA329014, NP\_005746.2, 219424.at  
 Figure 3686: PRO9998  
 Figure 3687: DNA328901, FLJ20533, 219449.s.at  
 Figure 3688: PRO84622  
 Figure 3689: DNA328902, NP\_071750.1, 219452.at  
 Figure 3690: PRO84623  
 Figure 3691: DNA328367, RIN3, 219456.s.at  
 Figure 3692: PRO84226  
 Figure 3693: DNA331598, AK026092, 219457.s.at  
 Figure 3694: PRO86601  
 Figure 3695: DNA327890, NP\_079021.1, 219493.at  
 Figure 3696: PRO83826  
 Figure 3697A-B: DNA227179, NP\_059120.1, 219505.at  
 Figure 3698: PRO37642  
 Figure 3699A-C: DNA331599, BCL11B, 219528.s.at  
 Figure 3700: PRO86602  
 Figure 3701: DNA329300, GEMIN6, 219539.at  
 Figure 3702: PRO84889  
 Figure 3703: DNA328908, 7691567.2, 219540.at  
 Figure 3704: PRO84629  
 Figure 3705: DNA256737, NP\_060276.1, 219541.at  
 Figure 3706: PRO51671  
 Figure 3707: DNA330410, NP\_060925.1, 219555.s.at  
 Figure 3708: PRO85618  
 Figure 3709A-B: DNA331600, NP\_061985.1, 219577.s.at  
 Figure 3710: PRO86603  
 Figure 3711: DNA325053, NP\_060230.2, 219588.s.at  
 Figure 3712: PRO81637  
 Figure 3713: DNA330412, NP\_057617.1, 219594.at  
 Figure 3714: PRO23600  
 Figure 3715: DNA331601, NP\_071915.1, 219628.at  
 Figure 3716: PRO85620  
 Figure 3717: DNA330414, NP\_057615.1, 219657.s.at  
 Figure 3718: PRO81138  
 Figure 3719A-B: DNA274044, HSM801565, 219671.at  
 Figure 3720: PRO61987  
 Figure 3721: DNA293243, RCP, 219681.s.at  
 Figure 3722: PRO70699  
 Figure 3723: DNA255161, NP\_071430.1, 219684.at  
 Figure 3724: PRO50241  
 Figure 3725: DNA287206, NP\_060124.1, 219691.at  
 Figure 3726: PRO69488  
 Figure 3727A-B: DNA330297, NP\_065138.2, 219700.at  
 Figure 3728: PRO85524  
 Figure 3729: DNA330416, TDP1, 219715.s.at  
 Figure 3730: PRO85622  
 Figure 3731: DNA330417, NP\_085144.1, 219716.at  
 Figure 3732: PRO21341  
 Figure 3733A-B: DNA227255, NP\_036579.1, 219753.at

Figure 3734: PRO37718  
 Figure 3735: DNA328919, NP\_078987.1, 219777.at  
 Figure 3736: PRO84637  
 Figure 3737A-B: DNA331602, NP\_060568.3, 219787.s.at  
 Figure 3738: PRO86604  
 Figure 3739: DNA255822, NP\_036346.1, 219797.at  
 Figure 3740: PRO50877  
 Figure 3741: DNA227305, NP\_064564.1, 219806.s.at  
 Figure 3742: PRO37768  
 Figure 3743: DNA329303, NP\_054737.1, 219819.s.at  
 Figure 3744: PRO84892  
 Figure 3745: DNA287295, NP\_078784.1, 219836.at  
 Figure 3746: PRO69564  
 Figure 3747: DNA287234, NP\_114174.1, 219862.s.at  
 Figure 3748: PRO69513  
 Figure 3749: DNA287221, NP\_057407.1, 219863.at  
 Figure 3750: PRO69500  
 Figure 3751: DNA330419, NP\_038469.1, 219864.s.at  
 Figure 3752: PRO85624  
 Figure 3753: DNA255255, LOC64116, 219869.s.at  
 Figure 3754: PRO50332  
 Figure 3755: DNA330420, NP\_078890.1, 219871.at  
 Figure 3756: PRO85625  
 Figure 3757: DNA256325, NP\_005470.1, 219889.at  
 Figure 3758: PRO51367  
 Figure 3759: DNA330421, NP\_057438.2, 219911.s.at  
 Figure 3760: PRO85626  
 Figure 3761A-B: DNA330422, NP\_057736.2, 219913.s.at  
 Figure 3762: PRO85627  
 Figure 3763: DNA227787, NP\_060606.1, 219918.s.at  
 Figure 3764: PRO38250  
 Figure 3765: DNA330423, NP\_037466.2, 219920.s.at  
 Figure 3766: PRO85628  
 Figure 3767A-B: DNA330424, LTBP3, 219922.s.at  
 Figure 3768: PRO85629  
 Figure 3769: DNA328924, NP\_057150.2, 219933.at  
 Figure 3770: PRO84641  
 Figure 3771: DNA218280, NP\_068570.1, 219971.at  
 Figure 3772: PRO34332  
 Figure 3773: DNA325979, NP\_060924.4, 219978.s.at  
 Figure 3774: PRO82424  
 Figure 3775: DNA330425, NP\_078956.1, 219990.at  
 Figure 3776: PRO85630  
 Figure 3777A-B: DNA330426, SGK1, 220038.at  
 Figure 3778: PRO85631  
 Figure 3779: DNA328926, NP\_064703.1, 220046.s.at  
 Figure 3780: PRO84643  
 Figure 3781A-B: DNA218680, NP\_071731.1, 220048.at  
 Figure 3782: PRO21724  
 Figure 3783: DNA330427, NP\_036593.1, 220052.s.at  
 Figure 3784: PRO85632  
 Figure 3785: DNA330428, NP\_060385.1, 220060.s.at  
 Figure 3786: PRO85633

Figure 3787: DNA330537, NP\_060533.2, 220085.at  
 Figure 3788: PRO81892  
 Figure 3789: DNA256091, NP\_071385.1, 220094.s.at  
 Figure 3790: PRO51141  
 Figure 3791: DNA330430, NP\_078945.1, 220112.at  
 Figure 3792: PRO85634  
 Figure 3793: DNA330431, NP\_055198.1, 220118.at  
 Figure 3794: PRO85635  
 Figure 3795: DNA227302, NP\_037401.1, 220132.s.at  
 Figure 3796: PRO37765  
 Figure 3797: DNA330432, NP\_079219.1, 220169.at  
 Figure 3798: PRO85636  
 Figure 3799: DNA331603, TMPRSS3, 220177.s.at  
 Figure 3800: PRO83482  
 Figure 3801: DNA256291, NP\_079182.1, 220232.at  
 Figure 3802: PRO51335  
 Figure 3803: DNA330434, NP\_060842.1, 220235.s.at  
 Figure 3804: PRO85637  
 Figure 3805: DNA330435, NP\_060179.1, 220306.at  
 Figure 3806: PRO85638  
 Figure 3807: DNA330436, NP\_037394.1, 220319.s.at  
 Figure 3808: PRO85639  
 Figure 3809: DNA327904, NP\_071419.2, 220330.s.at  
 Figure 3810: PRO83839  
 Figure 3811: DNA287186, NP\_061134.1, 220358.at  
 Figure 3812: PRO69472  
 Figure 3813A-B: DNA330437, NP\_079366.1, 220370.s.at  
 Figure 3814: PRO85640  
 Figure 3815: DNA330438, NP\_061026.1, 220485.s.at  
 Figure 3816: PRO50795  
 Figure 3817: DNA327214, NP\_078991.2, 220495.s.at  
 Figure 3818: PRO83483  
 Figure 3819: DNA324252, NP\_060444.1, 220521.s.at  
 Figure 3820: PRO80936  
 Figure 3821: DNA331604, PHEMX, 220558.x.at  
 Figure 3822: PRO86605  
 Figure 3823: DNA256363, NP\_057686.1, 220565.at  
 Figure 3824: PRO51405  
 Figure 3825: DNA255798, NP\_079265.1, 220576.at  
 Figure 3826: PRO50853  
 Figure 3827: DNA330440, NP\_079098.1, 220591.s.at  
 Figure 3828: PRO85642  
 Figure 3829: DNA255734, NP\_057607.1, 220646.s.at  
 Figure 3830: PRO50791  
 Figure 3831A-B: DNA327908, MCM10, 220651.s.at  
 Figure 3832: PRO83843  
 Figure 3833: DNA329306, NP\_079149.2, 220655.at  
 Figure 3834: PRO84895  
 Figure 3835A-B: DNA327909, ARNTL2, 220658.s.at  
 Figure 3836: PRO83844  
 Figure 3837: DNA329307, NP\_037483.1, 220684.at  
 Figure 3838: PRO84896  
 Figure 3839: DNA323756, NP\_057267.2, 220688.s.at  
 Figure 3840: PRO80512  
 Figure 3841: DNA331380, DKFZp566O084Homo, 220690.s.at  
 Figure 3842: DNA330442, NP\_054866.1, 220692.at  
 Figure 3843: PRO85643  
 Figure 3844: DNA330443, NP\_061086.1, 220702.at  
 Figure 3845: PRO85644  
 Figure 3846: DNA288247, NP\_478059.1, 220892.s.at  
 Figure 3847: PRO70011  
 Figure 3848: DNA327916, NP\_079466.1, 220940.at  
 Figure 3849: PRO83851  
 Figure 3850: DNA327953, NP\_055182.2, 220942.x.at  
 Figure 3851: PRO83878  
 Figure 3852: DNA327917, NP\_112240.1, 220966.x.at  
 Figure 3853: PRO83852  
 Figure 3854: DNA329078, VMP1, 220990.s.at  
 Figure 3855: PRO23253  
 Figure 3856A-B: DNA254516, NP\_112196.1, 220992.s.at  
 Figure 3857: PRO49623  
 Figure 3858: DNA330444, NP\_110405.1, 220999.s.at  
 Figure 3859: PRO85645  
 Figure 3860: DNA324246, NP\_112188.1, 221004.s.at  
 Figure 3861: PRO80930  
 Figure 3862: DNA330445, NP\_112174.1, 221012.s.at  
 Figure 3863: PRO85646  
 Figure 3864A-B: DNA254816, NP\_110444.1, 221031.s.at  
 Figure 3865: PRO49912  
 Figure 3866: DNA330446, NP\_054889.1, 221046.s.at  
 Figure 3867: PRO85647  
 Figure 3868: DNA330447, NP\_079174.1, 221080.s.at  
 Figure 3869: PRO85648  
 Figure 3870: DNA226227, NP\_060872.1, 221111.at  
 Figure 3871: PRO36690  
 Figure 3872: DNA227267, NP\_061130.1, 221123.x.at  
 Figure 3873: PRO37730  
 Figure 3874: DNA217256, NP\_065386.1, 221165.s.at  
 Figure 3875: PRO34298  
 Figure 3876: DNA329310, AK027224, 221185.s.at  
 Figure 3877: PRO84899  
 Figure 3878: DNA324408, NP\_060493.2, 221203.s.at  
 Figure 3879: PRO81072  
 Figure 3880A-B: DNA330448, NP\_059111.1, 221221.s.at  
 Figure 3881: PRO85649  
 Figure 3882: DNA331605, CISH, 221223.x.at  
 Figure 3883: PRO86458  
 Figure 3884: DNA330450, AK025947, 221235.s.at  
 Figure 3885: PRO85651  
 Figure 3886: DNA330451, NP\_110429.1, 221249.s.at  
 Figure 3887: PRO85652  
 Figure 3888: DNA330452, NP\_112494.2, 221258.s.at  
 Figure 3889: PRO85653  
 Figure 3890: DNA295327, NP\_068575.1, 221271.at  
 Figure 3891: PRO70773  
 Figure 3892: DNA330453, NP\_112597.1, 221277.s.at  
 Figure 3893: PRO85654

Figure 3894: DNA329312, NP\_005205.2, 221331.x.at  
 Figure 3895: PRO84901  
 Figure 3896: DNA288250, NP\_112487.1, 221434.s.at  
 Figure 3897: PRO70013  
 Figure 3898: DNA330454, NP\_112589.1, 221436.s.at  
 Figure 3899: PRO85655  
 Figure 3900: DNA330455, 1097190.16, 221477.s.at  
 Figure 3901: PRO85656  
 Figure 3902: DNA150865, NP\_057005.1, 221488.s.at  
 Figure 3903: PRO11587  
 Figure 3904: DNA272972, NP\_057356.1, 221496.s.at  
 Figure 3905: PRO61052  
 Figure 3906A-B: DNA329316, AF158555, 221510.s.at  
 Figure 3907: PRO84904  
 Figure 3908: DNA330456, NP\_060571.1, 221520.s.at  
 Figure 3909: PRO85657  
 Figure 3910: DNA326221, NP\_057179.1, 221521.s.at  
 Figure 3911: PRO82634  
 Figure 3912: DNA328953, NP\_004086.1, 221539.at  
 Figure 3913: PRO70296  
 Figure 3914: DNA329317, AF288571, 221558.s.at  
 Figure 3915: PRO81157  
 Figure 3916: DNA330457, NP\_076944.1, 221559.s.at  
 Figure 3917: PRO85658  
 Figure 3918: DNA329319, BC006401, 221601.s.at  
 Figure 3919: PRO1607  
 Figure 3920: DNA329319, NP\_005440.1, 221602.s.at  
 Figure 3921: PRO1607  
 Figure 3922: DNA254308, NP\_060950.1, 221622.s.at  
 Figure 3923: PRO49419  
 Figure 3924: DNA287254, NP\_077004.1, 221637.s.at  
 Figure 3925: PRO69528  
 Figure 3926: DNA330458, NP\_060634.1, 221652.s.at  
 Figure 3927: PRO85659  
 Figure 3928: DNA218280, IL21R, 221658.s.at  
 Figure 3929: PRO34332  
 Figure 3930: DNA327927, NP\_037390.2, 221666.s.at  
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 Figure 3936: DNA330460, NP\_060255.2, 221685.s.at  
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 Figure 3943: PRO84667  
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 Figure 3947: PRO23319  
 Figure 3948: DNA328964, AK056028, 221770.at  
 Figure 3949: PRO84669  
 Figure 3950: DNA330463, HSM801191, 221790.s.at  
 Figure 3951A-B: DNA151745, DNA151745, 221805.at  
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 Figure 3953: DNA274058, NP\_057203.1, 221816.s.at  
 Figure 3954: PRO61999  
 Figure 3955: DNA325039, NP\_004902.1, 221824.s.at  
 Figure 3956: PRO2733  
 Figure 3957: DNA273311, NP\_003022.1, 221833.at  
 Figure 3958: PRO61319  
 Figure 3959: DNA272419, AF105036, 221841.s.at  
 Figure 3960: PRO60672  
 Figure 3961: DNA330464, NP\_067082.1, 221882.s.at  
 Figure 3962: PRO85663  
 Figure 3963A-B: DNA330465, 253695.2, 221916.at  
 Figure 3964: PRO85664  
 Figure 3965A-B: DNA330466, AB018304, 221922.at  
 Figure 3966: DNA329321, NP\_112493.1, 221931.s.at  
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 Figure 3968: DNA330467, NP\_060114.1, 221986.s.at  
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 Figure 3970: DNA287235, FLJ10534, 221987.s.at  
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 Figure 3973: PRO62466  
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 Figure 3975: PRO86606  
 Figure 3976: DNA257797, DNA257797, 222036.s.at  
 Figure 3977: DNA257798, DNA257798, 222037.at  
 Figure 3978: DNA330468, 1454101.4, 222044.at  
 Figure 3979: PRO85666  
 Figure 3980: DNA329919, BC013365, 222045.s.at  
 Figure 3981: PRO85234  
 Figure 3982: DNA304466, NP\_004834.1, 222062.at  
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 Figure 3984: DNA325648, NP\_037409.2, 222077.s.at  
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 Figure 3986: DNA331386, HST000012, 222150.s.at  
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 Figure 3988: PRO69490  
 Figure 3989: DNA256784, NP\_075069.1, 222209.s.at  
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 Figure 3993: DNA330469, NP\_056249.1, 222250.s.at  
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 Figure 3995: DNA328885, EKI1, 222262.s.at  
 Figure 3996: PRO50294  
 Figure 3997: DNA330470, 096828.1, 222307.at  
 Figure 3998: PRO85668  
 Figure 3999: DNA330471, 027307.1, 222309.at  
 Figure 4000: PRO85669  
 Figure 4001: DNA330472, 128864.1, 222326.at  
 Figure 4002: PRO85670  
 Figure 4003: DNA330473, NP\_060676.2, 222387.s.at

- Figure 4004: PRO85671  
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 Figure 4018: PRO84557  
 Figure 4019: DNA331608, SNX5, 222417.s\_at  
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 Figure 4021: DNA326307, NP\_056399.1, 222425.s\_at  
 Figure 4022: PRO82707  
 Figure 4023: DNA227223, GK001, 222432.s\_at  
 Figure 4024: PRO37686  
 Figure 4025A-B: DNA329326, NP\_005110.1, 222439.s\_at  
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 Figure 4027: DNA327939, NP\_060654.1, 222442.s\_at  
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 Figure 4030: PRO84911  
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 Figure 4032: PRO51526  
 Figure 4033A-B: DNA225648, ERBB2IP, 222473.s\_at  
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 Figure 4035: DNA304460, BC003048, 222500.at  
 Figure 4036: PRO4984  
 Figure 4037: DNA330477, NP\_036227.1, 222516.at  
 Figure 4038: PRO37979  
 Figure 4039: DNA329328, NP\_067026.2, 222532.at  
 Figure 4040: PRO84912  
 Figure 4041: DNA16435, DNA16435, 222543.at  
 Figure 4042: PRO276  
 Figure 4043: DNA330478, NP\_056978.2, 222557.at  
 Figure 4044: PRO85675  
 Figure 4045A-B: DNA330479, 900264.1, 222572.at  
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 Figure 4053: PRO85679  
 Figure 4054: DNA329330, NP\_057130.1, 222609.s\_at  
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 Figure 4056A-B: DNA331609, 402471.3, 222613.at  
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 Figure 4059: PRO85681  
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 Figure 4061: PRO83870  
 Figure 4062: DNA327943, NP\_055399.1, 222646.s\_at  
 Figure 4063: PRO865  
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 Figure 4065: PRO61430  
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 Figure 4067: DNA330487, AB052751, 222696.at  
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 Figure 4072: DNA275116, DNA275116, 222726.s\_at  
 Figure 4073: DNA330489, BC019909, 222740.at  
 Figure 4074: PRO85683  
 Figure 4075: DNA330490, 399171.38, 222754.at  
 Figure 4076: PRO85684  
 Figure 4077: DNA330491, BC002522, 222759.at  
 Figure 4078: PRO85685  
 Figure 4079A-B: DNA330492, FLJ11294, 222763.s\_at  
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 Figure 4083: DNA330493, AK025248, 222770.s\_at  
 Figure 4084: PRO85687  
 Figure 4085: DNA304780, NETO2, 222774.s\_at  
 Figure 4086: PRO69889  
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 Figure 4089: DNA330495, NP\_060468.1, 222781.s\_at  
 Figure 4090: PRO85689  
 Figure 4091: DNA330496, HSM802366, 222793.at  
 Figure 4092: DNA330395, FLJ20281, 222816.s\_at  
 Figure 4093: PRO85603  
 Figure 4094A-B: DNA331610, TBDN100, 222837.s\_at  
 Figure 4095: PRO86609  
 Figure 4096: DNA330881, AB027233, 222838.at  
 Figure 4097: PRO1138  
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 Figure 4100: DNA273489, NP\_055210.1, 222858.s\_at  
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 Figure 4102: DNA273489, DAPP1, 222859.s\_at  
 Figure 4103: PRO61472  
 Figure 4104: DNA330498, NP\_036225.1, 222862.s\_at  
 Figure 4105: PRO85691  
 Figure 4106: DNA329336, NP\_057144.1, 222867.s\_at  
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 Figure 4111: PRO85692

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 Figure 4117: PRO85694  
 Figure 4118A-B: DNA330502, AB042719, 222962\_s\_at  
 Figure 4119: PRO85695  
 Figure 4120: DNA329337, AF279437, 222974\_at  
 Figure 4121: PRO10096  
 Figure 4122: DNA329338, 459502.10, 222977\_at  
 Figure 4123: PRO84921  
 Figure 4124A-B: DNA329339, 459502.5, 222978\_at  
 Figure 4125: PRO84922  
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 Figure 4128: DNA152786, NP\_057215.1, 222980\_at  
 Figure 4129: PRO10928  
 Figure 4130: DNA152786, RAB10, 222981\_s\_at  
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 Figure 4133: PRO10607  
 Figure 4134: DNA330503, NP\_038466.2, 222989\_s\_at  
 Figure 4135: PRO85696  
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 Figure 4139: PRO84923  
 Figure 4140: DNA329571, NP\_057547.3, 222996\_s\_at  
 Figure 4141: PRO51662  
 Figure 4142: DNA326195, NP\_054781.1, 223018\_at  
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 Figure 4145: PRO85697  
 Figure 4146A-B: DNA329342, AF172847, 223027\_at  
 Figure 4147: PRO84924  
 Figure 4148: DNA329344, FRSB, 223035\_s\_at  
 Figure 4149: PRO84926  
 Figure 4150: DNA330506, NP\_067061.1, 223038\_s\_at  
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 Figure 4153: PRO85698  
 Figure 4154: DNA287260, NP\_057184.1, 223040\_at  
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 Figure 4156: DNA324198, HSM801908, 223044\_at  
 Figure 4157: PRO37675  
 Figure 4158: DNA330508, AF116694, 223047\_at  
 Figure 4159: PRO85699  
 Figure 4160: DNA189412, NP\_057390.1, 223054\_at  
 Figure 4161: PRO25349  
 Figure 4162A-B: DNA256347, AF298880, 223055\_s\_at  
 Figure 4163: PRO51389  
 Figure 4164A-B: DNA329345, AB033117, 223056\_s\_at  
 Figure 4165: DNA327948, NP\_060394.1, 223060\_at  
 Figure 4166: PRO69660  
 Figure 4167: DNA288247, PSA, 223062\_s\_at  
 Figure 4168: PRO70011  
 Figure 4169: DNA330509, AK024555, 223066\_at  
 Figure 4170: PRO80652  
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 Figure 4172: PRO37757  
 Figure 4173: DNA331612, AF097492, 223079\_s\_at  
 Figure 4174: PRO86611  
 Figure 4175: DNA326258, NP\_077273.1, 223081\_at  
 Figure 4176: PRO82665  
 Figure 4177: DNA329346, AK027070, 223085\_at  
 Figure 4178: PRO84928  
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 Figure 4181: DNA331613, 238178.17, 223087\_at  
 Figure 4182: PRO86612  
 Figure 4183: DNA329347, NP\_060949.1, 223088\_x\_at  
 Figure 4184: PRO84929  
 Figure 4185: DNA330511, AK001338, 223090\_x\_at  
 Figure 4186: PRO85701  
 Figure 4187: DNA324209, NP\_057018.1, 223096\_at  
 Figure 4188: PRO80902  
 Figure 4189: DNA329349, NP\_054861.1, 223100\_s\_at  
 Figure 4190: PRO84931  
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 Figure 4192: PRO83852  
 Figure 4193: DNA330512, NP\_056494.1, 223109\_at  
 Figure 4194: PRO85702  
 Figure 4195: DNA330436, MIR, 223129\_x\_at  
 Figure 4196: PRO85639  
 Figure 4197: DNA330513, AF212221, 223130\_s\_at  
 Figure 4198: PRO85703  
 Figure 4199A-: DNA330514, DDX36, 223138\_s\_at  
 Figure 4200: PRO85704  
 Figure 4201A-: DNA330514, AF217190, 223139\_s\_at  
 Figure 4202: PRO85704  
 Figure 4203: DNA325557, NP\_115675.1, 223151\_at  
 Figure 4204: PRO82060  
 Figure 4205: DNA329352, NP\_057154.2, 223156\_at  
 Figure 4206: PRO84932  
 Figure 4207: DNA329353, NP\_113665.1, 223179\_at  
 Figure 4208: PRO84933  
 Figure 4209: DNA254276, NP\_054896.1, 223180\_s\_at  
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 Figure 4212: PRO83878  
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 Figure 4214: PRO66283  
 Figure 4215: DNA304467, NP\_115703.1, 223212\_at  
 Figure 4216: PRO71043  
 Figure 4217: DNA227267, LOC55893, 223216\_x\_at  
 Figure 4218: PRO37730

- Figure 4219: DNA327954, NP\_113646.1, 223220.s\_at  
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Figure 4223: DNA329321, SEC13L, 223225.s\_at  
Figure 4224: PRO84906  
Figure 4225: DNA247474, NP\_054895.1, 223229.at  
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Figure 4228: PRO85706  
Figure 4229: DNA287171, NP\_036312.1, 223240.at  
Figure 4230: PRO69462  
Figure 4231: DNA324046, NP\_115700.1, 223272.s\_at  
Figure 4232: PRO80763  
Figure 4233: DNA330517, NP\_115879.1, 223273.at  
Figure 4234: PRO85707  
Figure 4235: DNA330518, BC002493, 223274.at  
Figure 4236: PRO85708  
Figure 4237: DNA330519, NP\_060607.1, 223275.at  
Figure 4238: PRO85709  
Figure 4239: DNA330520, NP\_005777.2, 223283.s\_at  
Figure 4240: PRO85710  
Figure 4241: DNA330521, BC002762, 223286.at  
Figure 4242: PRO85711  
Figure 4243A-B: DNA330522, AF250920, 223287.s\_at  
Figure 4244: PRO85712  
Figure 4245: DNA330523, BC001220, 223294.at  
Figure 4246: PRO85713  
Figure 4247: DNA330524, MGC4268, 223297.at  
Figure 4248: PRO85714  
Figure 4249: DNA329356, NP\_115671.1, 223304.at  
Figure 4250: PRO84935  
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Figure 4252: PRO85655  
Figure 4253: DNA330526, NP\_115682.1, 223318.s\_at  
Figure 4254: PRO34564  
Figure 4255A-B: DNA330527, AF272663, 223319.at  
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Figure 4257: DNA329358, NP\_115649.1, 223334.at  
Figure 4258: PRO84937  
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Figure 4260: PRO50764  
Figure 4261: DNA330529, 241399.1, 223343.at  
Figure 4262: PRO85717  
Figure 4263A-B: DNA255756, HUMPE7A, 223358.s\_at  
Figure 4264: PRO50812  
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Figure 4266: PRO37588  
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Figure 4268: PRO38881  
Figure 4269A-B: DNA329360, NP\_115644.1, 223382.s\_at  
Figure 4270: PRO84939  
Figure 4271A-B: DNA329360, NIN283, 223383.at  
Figure 4272: PRO84939  
Figure 4273: DNA330531, NP\_037508.1, 223394.at  
Figure 4274: PRO85718  
Figure 4275: DNA329361, AF161528, 223397.s\_at  
Figure 4276: PRO84940  
Figure 4277: DNA324156, NP\_115588.1, 223403.s\_at  
Figure 4278: PRO80856  
Figure 4279A-B: DNA254516, C1orf25, 223404.s\_at  
Figure 4280: PRO49623  
Figure 4281: DNA256407, NP\_055188.1, 223423.at  
Figure 4282: PRO51448  
Figure 4283: DNA255676, HSM801648, 223434.at  
Figure 4284: PRO50738  
Figure 4285: DNA330532, NP\_078804.1, 223439.at  
Figure 4286: PRO85719  
Figure 4287: DNA330533, NP\_058647.1, 223451.s\_at  
Figure 4288: PRO772  
Figure 4289: DNA329365, CAB56010.1, 223452.s\_at  
Figure 4290: PRO84944  
Figure 4291: DNA327958, NP\_115789.1, 223484.at  
Figure 4292: PRO23554  
Figure 4293: DNA329456, NP\_057126.1, 223489.x\_at  
Figure 4294: PRO85023  
Figure 4295: DNA329456, RRP40, 223490.s\_at  
Figure 4296: PRO85023  
Figure 4297: DNA330534, AF307332, 223494.at  
Figure 4298: PRO85720  
Figure 4299: DNA304784, NP\_006564.1, 223502.s\_at  
Figure 4300: PRO738  
Figure 4301: DNA330535, NP\_115883.1, 223506.at  
Figure 4302: PRO85721  
Figure 4303: DNA330536, NP\_115666.1, 223542.at  
Figure 4304: PRO85722  
Figure 4305: DNA330537, AF155827, 223556.at  
Figure 4306: PRO81892  
Figure 4307A-B: DNA327908, HSM801808, 223570.at  
Figure 4308: PRO83843  
Figure 4309: DNA330538, AF262027, 223598.at  
Figure 4310: PRO85723  
Figure 4311: DNA330539, NP\_055411.1, 223639.s\_at  
Figure 4312: PRO85724  
Figure 4313: DNA330540, NP\_055081.1, 223640.at  
Figure 4314: PRO85725  
Figure 4315: DNA330541, AF277625, 223675.s\_at  
Figure 4316: PRO85726  
Figure 4317: DNA330542, NP\_115493.1, 223700.at  
Figure 4318: PRO85727  
Figure 4319: DNA330543, NAG73, 223725.at  
Figure 4320: PRO85728  
Figure 4321: DNA329367, TTYH2, 223741.s\_at  
Figure 4322: PRO84946  
Figure 4323: DNA331615, AB049635, 223743.s\_at  
Figure 4324: PRO62669  
Figure 4325: DNA188735, NP\_001506.1, 223758.s\_at  
Figure 4326: PRO26224

- Figure 4327: DNA287253, LOC85028, 223774\_at  
 Figure 4328: PRO69527  
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 Figure 4330: PRO86613  
 Figure 4331: DNA330544, NP\_277049.1, 223800\_s\_at  
 Figure 4332: PRO85729  
 Figure 4333: DNA256005, NP\_004842.1, 223806\_s\_at  
 Figure 4334: PRO51056  
 Figure 4335: DNA330545, AF233516, 223834\_at  
 Figure 4336: PRO70906  
 Figure 4337: DNA327200, NP\_114156.1, 223836\_at  
 Figure 4338: PRO1065  
 Figure 4339: DNA330546, AF132203, 223839\_s\_at  
 Figure 4340: PRO85730  
 Figure 4341: DNA330547, NP\_066014.1, 223849\_s\_at  
 Figure 4342: PRO85731  
 Figure 4343: DNA331392, NP\_004186.1, 223851\_s\_at  
 Figure 4344: PRO364  
 Figure 4345: DNA330548, NP\_115590.1, 223880\_x\_at  
 Figure 4346: PRO85732  
 Figure 4347A-B: DNA330522, FOXP1, 223936\_s\_at  
 Figure 4348: PRO85712  
 Figure 4349A-B: DNA330550, HSM801744, 223946\_at  
 Figure 4350: PRO85734  
 Figure 4351: DNA331393, D83532, 223961\_s\_at  
 Figure 4352: PRO86458  
 Figure 4353: DNA324248, SP110, 223980\_s\_at  
 Figure 4354: PRO80932  
 Figure 4355: DNA330551, BC009946, 223983\_s\_at  
 Figure 4356: PRO85735  
 Figure 4357: DNA330552, BC001104, 223984\_s\_at  
 Figure 4358: PRO85736  
 Figure 4359: DNA328847, NP\_056338.1, 223989\_s\_at  
 Figure 4360: PRO84579  
 Figure 4361: DNA331617, AF332652, 224046\_s\_at  
 Figure 4362: PRO86614  
 Figure 4363: DNA329369, AF293026, 224130\_s\_at  
 Figure 4364: PRO84948  
 Figure 4365: DNA330553, AF116653, 224148\_at  
 Figure 4366: DNA331618, AF231339, 224204\_x\_at  
 Figure 4367: PRO86615  
 Figure 4368: DNA330554, AF277993, 224211\_at  
 Figure 4369: PRO85737  
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 Figure 4371: PRO38082  
 Figure 4372: DNA324707, NP\_037369.1, 224232\_s\_at  
 Figure 4373: PRO81339  
 Figure 4374: DNA323935, NP\_060586.1, 224233\_s\_at  
 Figure 4375: PRO80668  
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 Figure 4377: PRO84949  
 Figure 4378A-B: DNA330555, HSM801768, 224308\_s\_at  
 Figure 4379: PRO85738  
 Figure 4380: DNA330556, NP\_061881.2, 224319\_s\_at  
 Figure 4381: PRO85739  
 Figure 4382: DNA330557, C20orf154, 224320\_s\_at  
 Figure 4383: PRO85740  
 Figure 4384: DNA330558, NP\_057588.1, 224330\_s\_at  
 Figure 4385: PRO84950  
 Figure 4386: DNA327949, MRP64, 224334\_s\_at  
 Figure 4387: PRO83874  
 Figure 4388A-B: DNA330559, BAB21791.1, 224336\_s\_at  
 Figure 4389: PRO85741  
 Figure 4390: DNA331619, BC010896, 224345\_x\_at  
 Figure 4391: PRO86616  
 Figure 4392: DNA331620, NDRG3, 224368\_s\_at  
 Figure 4393: PRO86617  
 Figure 4394: DNA272626, RIP5, 224376\_s\_at  
 Figure 4395: PRO60759  
 Figure 4396: DNA330560, NP\_510882.1, 224413\_s\_at  
 Figure 4397: PRO85742  
 Figure 4398: DNA330561, AF321617, 224416\_s\_at  
 Figure 4399: PRO85743  
 Figure 4400: DNA328323, NP\_114148.2, 224428\_s\_at  
 Figure 4401: PRO69531  
 Figure 4402: DNA331621, AF060225, 224437\_s\_at  
 Figure 4403: PRO86618  
 Figure 4404: DNA330562, NP\_115716.1, 224448\_s\_at  
 Figure 4405: PRO85744  
 Figure 4406: DNA330563, NP\_113668.1, 224450\_s\_at  
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 Figure 4414: DNA329373, NP\_115722.1, 224467\_s\_at  
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 Figure 4416: DNA330567, NP\_116114.1, 224504\_s\_at  
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 Figure 4432: DNA329376, BAA91036.1, 224632\_at  
 Figure 4433: PRO84954  
 Figure 4434: DNA330572, CAB82324.1, 224648\_at

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 Figure 4448: PRO80871  
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 Figure 4546: DNA329397, NP\_114109.1, 225260.s.at  
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 Figure 4745A-B: DNA259025, DNA259025, 226180.at  
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 Figure 4747: DNA56350, DNA56350, 226181.at  
 Figure 4748: PRO956  
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Figure 4780: PRO85844  
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Figure 4782: PRO85845  
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Figure 4798: PRO85850  
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Figure 4800: PRO69688  
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- Figure 4863: DNA330564, ARHGAP9, 226906.s.at  
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 Figure 4908: DNA330714, 034544.1, 227198.at  
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 Figure 4933: PRO34697  
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 Figure 4953: PRO85894  
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 Figure 4989: PRO12022  
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 Figure 4994: PRO54411  
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 Figure 5058: PRO54700  
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 Figure 5066: DNA194202, DNA194202, 228370.at  
 Figure 5067: PRO23594  
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 Figure 5105: PRO85936  
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 Figure 5107: PRO85937  
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 Figure 5109: PRO85938  
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 Figure 5118: PRO51520  
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 Figure 5159: PRO85959  
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 Figure 5163: DNA328919, FLJ22690, 229367.s.at  
 Figure 5164: PRO84637  
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 Figure 5166: DNA268708, DNA268708, 229391.s.at  
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 Figure 5184: PRO83478  
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 Figure 5186: PRO36784

- Figure 5187A-B: DNA330802, 7694410.1, 229686.at  
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 Figure 5190: PRO86663  
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 Figure 5194: PRO86664  
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 Figure 5211: PRO85975  
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 Figure 5214: DNA330813, 246201.1, 230036.at  
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 Figure 5217: PRO52596  
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 Figure 5223: PRO85979  
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 Figure 5225: PRO88  
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 Figure 5227: PRO85980  
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 Figure 5229: PRO24061  
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 Figure 5237: PRO85983  
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 Figure 5243: PRO86666  
 Figure 5244: DNA331672, 332195.1, 230391.at  
 Figure 5245: PRO86667  
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 Figure 5259: DNA330829, 007717.1, 230580.at  
 Figure 5260: PRO85993  
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 Figure 5264: PRO85994  
 Figure 5265A-B: DNA328499, SORL1, 230707.at  
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 Figure 5267A-B: DNA328099, 335889.1, 230779.at  
 Figure 5268: PRO84009  
 Figure 5269: DNA194391, HSM800477, 230848.s.at  
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 Figure 5772: DNA331020, 403459.1, 242261.at  
 Figure 5773: PRO86178  
 Figure 5774: DNA331021, 017309.1, 242268.at  
 Figure 5775: PRO86179  
 Figure 5776: DNA331022, BC009627, 242304.at  
 Figure 5777: DNA331023, 119753.1, 242362.at  
 Figure 5778: PRO86181  
 Figure 5779: DNA331024, 028992.1, 242388.x.at  
 Figure 5780: PRO86182  
 Figure 5781: DNA328220, 239839.1, 242405.at  
 Figure 5782: PRO84123  
 Figure 5783: DNA331025, 127891.1, 242457.at  
 Figure 5784: PRO86183  
 Figure 5785: DNA328221, 221374.1, 242471.at  
 Figure 5786: PRO84124  
 Figure 5787: DNA257874, DNA257874, 242517.at  
 Figure 5788: DNA331026, 014632.1, 242518.at  
 Figure 5789: PRO86184  
 Figure 5790: DNA331027, 053796.1, 242560.at  
 Figure 5791: PRO86185  
 Figure 5792: DNA331028, 7693434.1, 242606.at  
 Figure 5793: PRO86186  
 Figure 5794: DNA331706, 351474.1, 242617.at

Figure 5795: PRO86701  
 Figure 5796: DNA331707, 330870.5, 242625.at  
 Figure 5797: PRO86702  
 Figure 5798: DNA331030, 407930.2, 242648.at  
 Figure 5799: PRO86188  
 Figure 5800: DNA331031, 405967.1, 242669.at  
 Figure 5801: PRO86189  
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 Figure 5803: PRO86703  
 Figure 5804A-C: DNA331033, AF330045, 242722.at  
 Figure 5805: PRO86191  
 Figure 5806: DNA331034, 7689086.1, 242735.x.at  
 Figure 5807: PRO86192  
 Figure 5808: DNA331035, 210512.1, 242783.at  
 Figure 5809: PRO86193  
 Figure 5810: DNA331036, 360991.1, 242836.at  
 Figure 5811: PRO86194  
 Figure 5812: DNA328224, 028975.1, 242859.at  
 Figure 5813: PRO84127  
 Figure 5814: DNA331037, 206873.1, 242890.at  
 Figure 5815: PRO86195  
 Figure 5816: DNA331709, 017276.1, 242903.at  
 Figure 5817: PRO86704  
 Figure 5818: DNA331710, 227540.15, 242960.at  
 Figure 5819: PRO86705  
 Figure 5820: DNA331711, 427600.1, 243006.at  
 Figure 5821: PRO86706  
 Figure 5822: DNA331041, 982079.2, 243030.at  
 Figure 5823: PRO86199  
 Figure 5824: DNA331042, 019764.1, 243037.at  
 Figure 5825: PRO86200  
 Figure 5826: DNA331043, 005042.1, 243134.at  
 Figure 5827: PRO86201  
 Figure 5828: DNA331044, 226264.10, 243154.at  
 Figure 5829: PRO86202  
 Figure 5830: DNA331045, 066434.1, 243222.at  
 Figure 5831: PRO86203  
 Figure 5832: DNA331712, 005752.1, 243271.at  
 Figure 5833: PRO86707  
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 Figure 5835: DNA331048, 7688599.1, 243366.s.at  
 Figure 5836: PRO86206  
 Figure 5837: DNA331049, 402027.4, 243395.at  
 Figure 5838: PRO86207  
 Figure 5839: DNA331713, 982999.2, 243423.at  
 Figure 5840: PRO86708  
 Figure 5841: DNA331051, 306804.1, 243469.at  
 Figure 5842: PRO86209  
 Figure 5843: DNA331714, 332965.1, 243496.at  
 Figure 5844: PRO86709  
 Figure 5845: DNA331053, 243689.1, 243509.at  
 Figure 5846: PRO86211  
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 Figure 5848: PRO86710  
 Figure 5849: DNA331055, 1512996.3, 243561.at

- Figure 5850: PRO86213  
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 Figure 5853: PRO86214  
 Figure 5854: DNA194184, DNA194184, 243764.at  
 Figure 5855: PRO23576  
 Figure 5856: DNA331057, 031316.1, 243888.at  
 Figure 5857: PRO86215  
 Figure 5858: DNA331058, 400813.1, 243918.at  
 Figure 5859: PRO86216  
 Figure 5860: DNA331059, 035870.32, 243934.at  
 Figure 5861: PRO86217  
 Figure 5862: DNA210271, DNA210271, 243999.at  
 Figure 5863: PRO33803  
 Figure 5864A-B: DNA331060, 406931.1, 244008.at  
 Figure 5865: PRO86218  
 Figure 5866: DNA331061, 198683.4, 244026.at  
 Figure 5867: PRO86219  
 Figure 5868: DNA331062, BC021973, 244052.at  
 Figure 5869: PRO23771  
 Figure 5870: DNA331716, 212607.1, 244267.at  
 Figure 5871: PRO86711  
 Figure 5872: DNA331064, 006039.1, 244313.at  
 Figure 5873: PRO86221  
 Figure 5874: DNA108738, DNA108738, 244321.at  
 Figure 5875: PRO9822  
 Figure 5876: DNA331065, 341348.1, 244382.at  
 Figure 5877: PRO86222  
 Figure 5878: DNA331066, 207228.1, 244443.at  
 Figure 5879: PRO86223  
 Figure 5880: DNA328239, 331922.4, 244450.at  
 Figure 5881: PRO84142  
 Figure 5882: DNA331067, 164869.1, 244599.at  
 Figure 5883: PRO86224  
 Figure 5884: DNA331068, 337465.1, 244677.at  
 Figure 5885: PRO86225  
 Figure 5886: DNA329512, 336575.1, 244780.at  
 Figure 5887: PRO85073  
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 Figure 5889: PRO86226  
 Figure 5890: DNA331070, 393412.1, 244801.at  
 Figure 5891: PRO86227  
 Figure 5892: DNA331071, 343563.1, 244869.at  
 Figure 5893: PRO86228  
 Figure 5894A-B: DNA254566, BAA11502.1, D80007.at  
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 Figure 5896: DNA328961, BC011049, DNA36995.at  
 Figure 5897: PRO84667  
 Figure 5898A-B: DNA331072, AB046821, DNA53991.at  
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 Figure 5901: DNA327205, GBP5, DNA61875.at  
 Figure 5902: PRO83478  
 Figure 5903: DNA331717, BC020203, DNA71289.at  
 Figure 5904: PRO86712  
 Figure 5905: DNA331718, AK024409, DNA92232.at  
 Figure 5906: PRO86713  
 Figure 5907: DNA96866, DNA96866, DNA96866.at  
 Figure 5908: PRO6015  
 Figure 5909: DNA331073, BC011775, DNA101926.at  
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 Figure 5911: DNA108670, DNA108670, DNA108670.at  
 Figure 5912: PRO7171  
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 Figure 5914: PRO71043  
 Figure 5915A-B: DNA108728, DNA108728, DNA108728.at  
 Figure 5916: PRO9741  
 Figure 5917: DNA329215, ICOS, DNA108917.at  
 Figure 5918: PRO7424  
 Figure 5919: DNA331719, BC002424, DNA143288.at  
 Figure 5920: PRO12705  
 Figure 5921A-B: DNA150956, HUMORFKG1P, DNA150956.at  
 Figure 5922: DNA330417, APOL6, DNA164989.at  
 Figure 5923: PRO21341  
 Figure 5924: DNA329483, AF384857, DNA166819.at  
 Figure 5925: PRO20110  
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 Figure 5927: PRO180  
 Figure 5928: DNA304468, NP\_077300.1, P\_Z93700.at  
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 Figure 5930: DNA39423, DNA39423, P\_X52252.at  
 Figure 5931: PRO271  
 Figure 5932: DNA330262, GW112, P\_Z64962.at  
 Figure 5933: PRO85493  
 Figure 5934: DNA331074, AF252257, P\_A37030.at  
 Figure 5935: DNA60764, DNA60764, P\_A46906.at  
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 Figure 5937: DNA331720, AF289594, P\_A37063.at  
 Figure 5938: PRO86714  
 Figure 5939: DNA331721, BC017876, P\_A37079.at  
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 Figure 5941: DNA76401, DNA76401, P\_A37126.at  
 Figure 5942: PRO1575  
 Figure 5943: DNA304475, NP\_116246.1, P\_A37128.at  
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 Figure 5945: DNA66480, HSAPO1, NM\_000043.at  
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 Figure 5949: DNA325712, CDK4, NM\_000075.at  
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 Figure 5955: DNA331723, U66095, NM\_000161.at

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Figure 5964: PRO86716  
Figure 5965A-B: DNA88419, HSINTA6R, NM\_000210.at  
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Figure 5967: DNA88428, HUMLAP, NM\_000211.at  
Figure 5968: PRO2787  
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Figure 5981: PRO37544  
Figure 5982: DNA76512, HSIL2REC, NM\_000417.at  
Figure 5983: PRO2020  
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Figure 5996: DNA36718, HUMIL10, NM\_000572.at  
Figure 5997: PRO73  
Figure 5998: DNA324158, NP\_000567.1, NM\_000576.at

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Figure 6001: PRO25194  
Figure 6002: DNA290585, NP\_000573.1, NM\_000582.f.at  
Figure 6003: PRO70536  
Figure 6004: DNA216500, NP\_000575.1, NM\_000584.at  
Figure 6005: PRO34252  
Figure 6006: DNA36712, HUMIL3, NM\_000588.at  
Figure 6007: PRO67  
Figure 6008A-B: DNA331733, AF361105, NM\_000590.at  
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Figure 6010: PRO36996  
Figure 6011A-B: DNA331735, AY066019, NM\_000594.at  
Figure 6012A-B: DNA331736, AY070490, NM\_000595.at  
Figure 6013: DNA331737, BC009902, NM\_000597.at  
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Figure 6016: PRO34288  
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Figure 6033: PRO2907  
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NM\_000877.at  
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Figure 6066: PRO12242  
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Figure 6070: PRO37015  
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Figure 6078: PRO1574  
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Figure 6080: PRO4936  
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Figure 6082: PRO12467  
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Figure 6084: PRO12867  
Figure 6085A-C: DNA331746, AF043045, NM\_001457.at

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Figure 6089: DNA227173, HSU93049, NM\_001465.at  
Figure 6090: PRO37636  
Figure 6091A-B: DNA331747, GABBR1, NM\_001470.at  
Figure 6092: PRO86724  
Figure 6093A-B: DNA76503, IL10RA, NM\_001558.at  
Figure 6094: PRO2536  
Figure 6095A-B: DNA227750, IL12RB2, NM\_001559.at  
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Figure 6097: DNA76556, HSU03397, NM\_001561.at  
Figure 6098: PRO2023  
Figure 6099: DNA82362, CXCL10, NM\_001565.at  
Figure 6100: PRO1718  
Figure 6101: DNA227013, NP\_001560.1, NM\_001569.at  
Figure 6102: PRO37476  
Figure 6103: DNA331748, BC009799, NM\_001657.at  
Figure 6104: PRO46  
Figure 6105: DNA150716, HSZNFNPRA, NM\_001706.at  
Figure 6106: PRO12790  
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Figure 6109: DNA150718, NP\_001727.1, NM\_001736.at  
Figure 6110: PRO12435  
Figure 6111A-B: DNA226387, HSCYCLF, NM\_001761.at  
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Figure 6114: PRO4912  
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Figure 6116: PRO4695  
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Figure 6122: PRO36899  
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Figure 6127: DNA227232, SLC31A1, NM\_001859.at  
Figure 6128: PRO37695  
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Figure 6137: DNA83048, DEFA4, NM\_001925.at  
Figure 6138: PRO2057  
Figure 6139: DNA88215, NP\_001919.1, NM\_001928.at  
Figure 6140: PRO2703  
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Figure 6142: PRO25042  
Figure 6143: DNA226871, NP\_001942.1, NM\_001951.at  
Figure 6144: PRO37334  
Figure 6145: DNA227332, NP\_001943.1, NM\_001952.at  
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Figure 6147: DNA225661, ECGF1, NM\_001953.at  
Figure 6148: PRO36124  
Figure 6149: DNA273174, HSEF1DELA, NM\_001960.at  
Figure 6150: PRO61211  
Figure 6151: DNA150779, HUMETR103, NM\_001964.at  
Figure 6152: PRO12798  
Figure 6153: DNA331753, HUMENOG, NM\_001975.at  
Figure 6154: PRO38010  
Figure 6155: DNA331754, BC002464, NM\_001992.at  
Figure 6156: PRO86728  
Figure 6157: DNA331755, D83920, NM\_002003.at  
Figure 6158: PRO86729  
Figure 6159: DNA226881, HUMERGBFLI, NM\_002017.at  
Figure 6160: PRO37344  
Figure 6161: DNA88332, FVT1, NM\_002035.at  
Figure 6162: PRO2753  
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Figure 6164: PRO36442  
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Figure 6168: PRO2768  
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Figure 6170: PRO38477  
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Figure 6172: PRO86730  
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Figure 6183: DNA103215, NP\_002210.1, NM\_002219.at  
Figure 6184: PRO4545  
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Figure 6194: DNA326343, BC003572, NM\_002265.at  
Figure 6195: PRO82739  
Figure 6196: DNA288243, LAG3, NM\_002286.at  
Figure 6197: PRO36451  
Figure 6198A-B: DNA188301, LIF, NM\_002309.at  
Figure 6199: PRO21834  
Figure 6200A-B: DNA331762, HUMLYTOXBB, NM\_002341.at  
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Figure 6208: PRO11598  
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Figure 6211: DNA103283, MNDA, NM\_002432.at  
Figure 6212: PRO4613  
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Figure 6214: PRO4852  
Figure 6215A-B: DNA331763, AF058696, NM\_002485.at  
Figure 6216: PRO36001  
Figure 6217: DNA103382, HSU49395, NM\_002561.at  
Figure 6218: PRO4711  
Figure 6219A-B: DNA88331, HSFUR, NM\_002569.at  
Figure 6220: PRO2752  
Figure 6221: DNA103488, PCNA, NM\_002592.at  
Figure 6222: PRO4815  
Figure 6223: DNA328587, NP\_002612.1, NM\_002621.at  
Figure 6224: PRO2854  
Figure 6225: DNA331764, NP\_071438.1,

NM\_002624.at  
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 Figure 6227: DNA227067, HSPKCB1A, NM\_002738.at  
 Figure 6228: PRO37530  
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 Figure 6230: PRO37553  
 Figure 6231: DNA88626, HUMSAPABCD, NM\_002778.at  
 Figure 6232: PRO2875  
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 Figure 6234: PRO84749  
 Figure 6235: DNA326853, NP\_002818.1, NM\_002827.at  
 Figure 6236: PRO38066  
 Figure 6237: DNA88607, NP\_002892.1, NM\_002901.at  
 Figure 6238: PRO2863  
 Figure 6239: DNA331765, AF294009, NM\_002934.at  
 Figure 6240: PRO2444  
 Figure 6241: DNA331766, AF043339, NM\_002983.at  
 Figure 6242: DNA51778, HSHC21, NM\_002984.at  
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 Figure 6244: DNA330124, CCL22, NM\_002990.at  
 Figure 6245: PRO34107  
 Figure 6246: DNA227788, NP\_002995.1, NM\_003004.at  
 Figure 6247: PRO38251  
 Figure 6248: DNA329005, HSU133017, NM\_003037.at  
 Figure 6249: PRO12612  
 Figure 6250: DNA196489, HUMMCT, NM\_003051.at  
 Figure 6251: PRO24980  
 Figure 6252A-B: DNA103542, HSLR11, NM\_003105.at  
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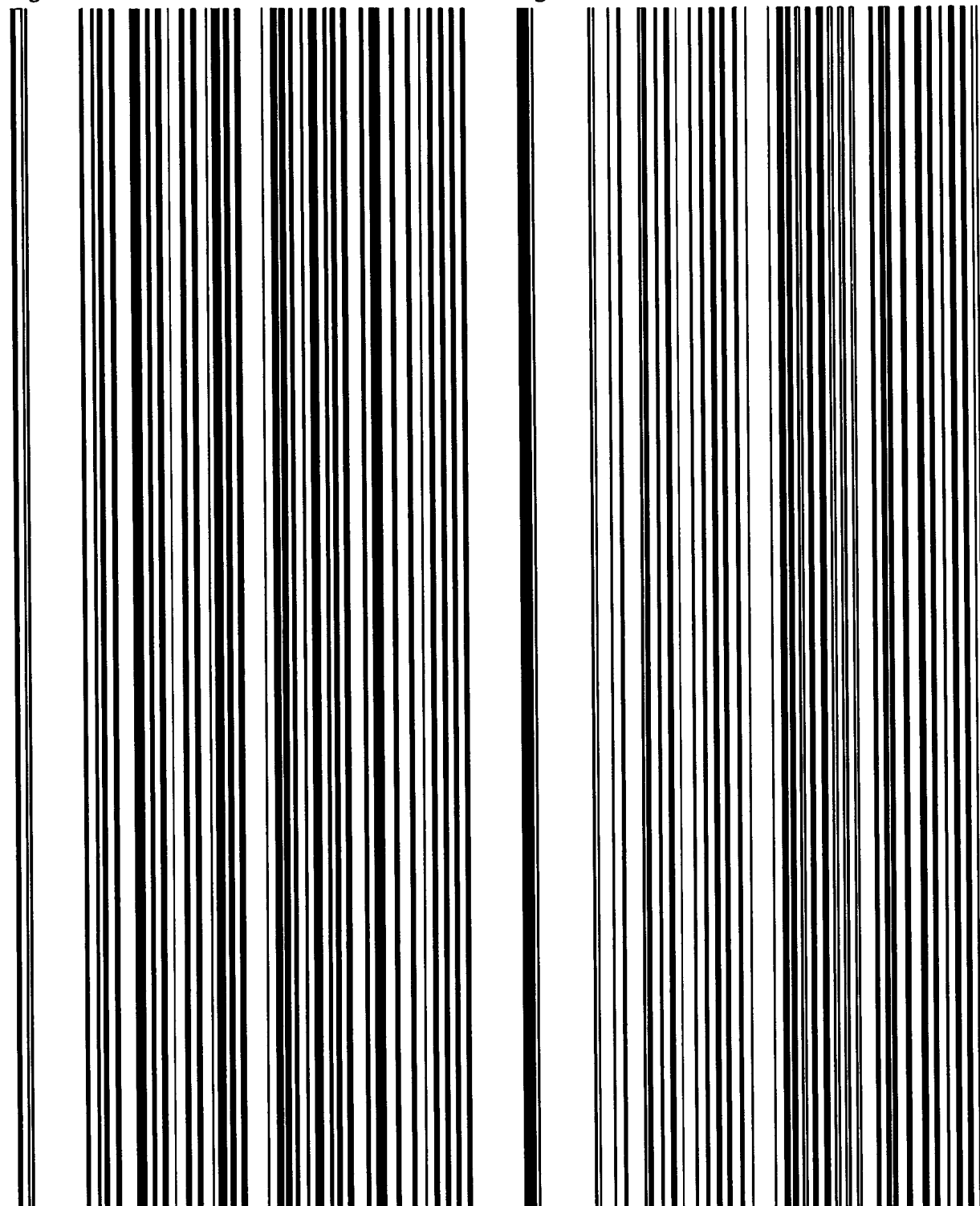
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Figure 7241: PRO58372  
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Figure 7244: DNA331902, BC014522, HSSOM172M.at  
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Figure 7253: DNA329041, HSM800399, AF132199.at  
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Figure 7257: PRO50012  
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Figure 7259: PRO85636  
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Figure 7265: PRO86273  
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Figure 7267: PRO51015  
Figure 7268: DNA255465, AK024313, AK024313.at  
Figure 7269: PRO50532  
Figure 7270: DNA329597, AK022178, AK022178.at  
Figure 7271: PRO85129  
Figure 7272: DNA254228, NP\_079236.1, AK021791.at  
Figure 7273: PRO49340  
Figure 7274: DNA331904, AK023431, AF298880.at  
Figure 7275: PRO86791  
Figure 7276: DNA329078, AF214006, HSM801679.at  
Figure 7277: PRO23253  
Figure 7278: DNA256784, FLJ22104, AK025757.at  
Figure 7279: PRO51716  
Figure 7280: DNA331905, AK001823, HSM801648.at  
Figure 7281: PRO86792  
Figure 7282: DNA329044, NP\_064562.1, AK025265.at  
Figure 7283: PRO84709  
Figure 7284: DNA331906, HSA227916, NM\_001530.at  
Figure 7285: DNA330023, GADD45A, NM\_001924.at  
Figure 7286: PRO85308  
Figure 7287A-B: DNA272191, RSN, NM\_002956.at  
Figure 7288: PRO60456  
Figure 7289: DNA328418, HUMG0S24A, NM\_003407.at  
Figure 7290: PRO84261  
Figure 7291: DNA331133, HSU63830, NM\_004180.at  
Figure 7292: PRO86274  
Figure 7293: DNA271310, DUSP8, NM\_004420.at  
Figure 7294: PRO59617  
Figure 7295: DNA331907, AKAP7, NM\_004842.at  
Figure 7296: PRO63228  
Figure 7297: DNA287203, NP\_006182.1, NM\_006191.at  
Figure 7298: PRO69487  
Figure 7299: DNA274783, HSU26424, NM\_006281.at  
Figure 7300: PRO62549  
Figure 7301A-B: DNA255281, NP\_006380.1, NM\_006389.at  
Figure 7302: PRO50357  
Figure 7303: DNA328712, NP\_006501.1, NM\_006510.at  
Figure 7304: PRO84469  
Figure 7305: DNA331908, AF161440, NM\_012111.at  
Figure 7306: DNA330065, STK18, NM\_014264.at  
Figure 7307: PRO85345  
Figure 7308: DNA152148, DNA152148, HSP1CDC21.at  
Figure 7309: PRO10290  
Figure 7310: DNA329925, HSBP1, NM\_001537.at  
Figure 7311: PRO85239  
Figure 7312: DNA331909, HSCFANT, NM\_002964.at  
Figure 7313: PRO86795  
Figure 7314: DNA329139, NP\_003893.2, NM\_003902.at  
Figure 7315: PRO84774  
Figure 7316: DNA331910, HSSEC232, NM\_006363.at

- Figure 7317: PRO86796  
 Figure 7318: DNA329047, BATF, NM\_006399\_at  
 Figure 7319: PRO58425  
 Figure 7320: DNA274167, AF026166, NM\_006431\_at  
 Figure 7321: PRO62097  
 Figure 7322: DNA254572, NP\_006576.1, NM\_006585\_at  
 Figure 7323: PRO49675  
 Figure 7324A-B: DNA331911, AB003334, NM\_006644\_at  
 Figure 7325: PRO86797  
 Figure 7326: DNA331912, BC009405, NM\_013411\_at  
 Figure 7327: PRO86798  
 Figure 7328: DNA255289, MELK, NM\_014791\_at  
 Figure 7329: PRO50363  
 Figure 7330A-B: DNA331913, BAB21784.1, NM\_015383\_at  
 Figure 7331: PRO86799  
 Figure 7332: DNA329148, LOC51042, NM\_015871\_at  
 Figure 7333: PRO84782  
 Figure 7334: DNA326221, AF125098, NM\_016095\_at  
 Figure 7335: PRO82634  
 Figure 7336: DNA331914, BC009398, HUMPCDC47\_at  
 Figure 7337: PRO86800  
 Figure 7338A-B: DNA328312, HUMAREB6, HUMAREB6\_at  
 Figure 7339: PRO84180  
 Figure 7340: DNA325941, HSPCA, HSHSP90R\_at  
 Figure 7341: PRO82388  
 Figure 7342: DNA328483, VIT1, NM\_000179\_at  
 Figure 7343: PRO84309  
 Figure 7344: DNA271847, HUMDNAJHOM, NM\_001539\_at  
 Figure 7345: PRO60127  
 Figure 7346: DNA331915, BC001786, NM\_002014\_at  
 Figure 7347: PRO59262  
 Figure 7348: DNA331916, HUMMIF, NM\_002415\_at  
 Figure 7349: DNA331917, PHF1, NM\_002636\_at  
 Figure 7350: PRO86802  
 Figure 7351: DNA329604, SRP54, NM\_003136\_at  
 Figure 7352: PRO85134  
 Figure 7353A-B: DNA331134, NP\_003381.1, NM\_003390\_at  
 Figure 7354: PRO86275  
 Figure 7355A-B: DNA290265, ZNF91, NM\_003430\_f.at  
 Figure 7356: PRO70395  
 Figure 7357A-C: DNA331918, AF009425, NM\_004338\_at  
 Figure 7358: PRO86803  
 Figure 7359: DNA254582, NP\_004626.1, NM\_004635\_at  
 Figure 7360: PRO49685  
 Figure 7361A-B: DNA275334, NP\_112162.1, NM\_004749\_at  
 Figure 7362: PRO63009  
 Figure 7363: DNA254157, HSU13045, NM\_005254\_at  
 Figure 7364: PRO49271  
 Figure 7365A-B: DNA124122, RBL2, NM\_005611\_at  
 Figure 7366: PRO6323  
 Figure 7367: DNA330776, TOB1, NM\_005749\_at  
 Figure 7368: PRO58014  
 Figure 7369: DNA326980, AF140598, NM\_014248\_at  
 Figure 7370: PRO83289  
 Figure 7371: DNA271608, HUMRSC419, NM\_014670\_at  
 Figure 7372: PRO59895  
 Figure 7373: DNA272928, HUMORFKG1F, NM\_014764\_at  
 Figure 7374: PRO61012  
 Figure 7375: DNA290235, NP\_057121.1, NM\_016037\_at  
 Figure 7376: PRO70335  
 Figure 7377: DNA331135, HUMKG1DD, HUMKG1DD\_at  
 Figure 7378A-B: DNA330119, AF226044, HUMKIAAQ\_at  
 Figure 7379: PRO85381  
 Figure 7380: DNA331137, HS24P52, HUMHSP70H.at  
 Figure 7381: PRO86278  
 Figure 7382A-B: DNA269805, NP\_001263.1, NM\_001272\_at  
 Figure 7383: PRO58209  
 Figure 7384: DNA270689, HSGATA3R, NM\_002051\_at  
 Figure 7385: PRO59053  
 Figure 7386: DNA331919, HUMCFA, NM\_002965\_at  
 Figure 7387: PRO80648  
 Figure 7388A-B: DNA304800, NP\_004146.1, NM\_004155\_at  
 Figure 7389: PRO69458  
 Figure 7390: DNA273418, AAG01157.1, NM\_004301\_at  
 Figure 7391: PRO61417  
 Figure 7392: DNA330066, MLLT3, NM\_004529\_at  
 Figure 7393: PRO85346  
 Figure 7394: DNA270733, S46622, NM\_005605\_at  
 Figure 7395: PRO59094  
 Figure 7396: DNA331138, NP\_005997.2, NM\_006006\_at  
 Figure 7397: PRO86279  
 Figure 7398: DNA331139, NP\_006865.1, NM\_006874\_at  
 Figure 7399: PRO81172  
 Figure 7400: DNA331920, AF090950, NM\_015675\_at  
 Figure 7401: PRO84384  
 Figure 7402: DNA329050, MRPS17, NM\_015969\_at  
 Figure 7403: PRO84712  
 Figure 7404A-B: DNA329122, GS3955, NM\_021643\_at

- Figure 7405: PRO84764  
 Figure 7406: DNA331921, 244055.1, AF320911.at  
 Figure 7407: PRO86804  
 Figure 7408: DNA331922, AK026275, AK026275.at  
 Figure 7409: PRO86805  
 Figure 7410A-B: DNA254516, AF288399, AF288399.at  
 Figure 7411: PRO49623  
 Figure 7412: DNA328313, NP\_115579.1, AK025076.at  
 Figure 7413: PRO84181  
 Figure 7414: DNA327865, NP\_079105.1, AK026315.at  
 Figure 7415: PRO83806  
 Figure 7416: DNA294813, NP\_444283.1, P\_T67134.at  
 Figure 7417: PRO70763  
 Figure 7418A-B: DNA254706, AB046851, AB046851.at  
 Figure 7419: DNA329052, NP\_078801.1, AK026237.at  
 Figure 7420: PRO84714  
 Figure 7421: DNA256890, BC008988, P\_Z00467.at  
 Figure 7422: PRO51824  
 Figure 7423: DNA256291, FLJ21032, AK024685.f.at  
 Figure 7424: PRO51335  
 Figure 7425: DNA331923, HSUCP2X12, P\_C69111.at  
 Figure 7426: DNA213665, DNA213665, P\_X30166.at  
 Figure 7427: PRO35126  
 Figure 7428: DNA331140, 332752.10, AK023798.at  
 Figure 7429: PRO86280  
 Figure 7430A-B: DNA331141, BAB13420.1, AB046814.at  
 Figure 7431: PRO86281  
 Figure 7432: DNA331924, BC004932, AK024551.at  
 Figure 7433: PRO21434  
 Figure 7434A-B: DNA256267, AB046838, AB046838.at  
 Figure 7435: DNA327954, BAL, P\_D00629.at  
 Figure 7436: PRO83879  
 Figure 7437: DNA255798, FLJ12377, AK022439.at  
 Figure 7438: PRO50853  
 Figure 7439: DNA330389, FLJ12888, AK022950.at  
 Figure 7440: PRO85598  
 Figure 7441: DNA330086, FLJ12973, AK023035.at  
 Figure 7442: PRO85360  
 Figure 7443: DNA331142, NP\_116325.1, P\_Z98137.at  
 Figure 7444: PRO51781  
 Figure 7445: DNA329384, BC008502, P\_Z33372.at  
 Figure 7446: PRO84960  
 Figure 7447A-B: DNA331143, NP\_149075.2, AK022613.at  
 Figure 7448: PRO86282  
 Figure 7449: DNA331925, 424693.10, AK022231.at  
 Figure 7450: PRO86806  
 Figure 7451: DNA331144, NP\_078834.1, AK023982.at  
 Figure 7452: PRO86283  
 Figure 7453A-B: DNA331926, BAB13449.1, AB046843.at  
 Figure 7454: PRO51258  
 Figure 7455: DNA255197, DNA255197, P\_Z50392.at  
 Figure 7456: PRO50276  
 Figure 7457: DNA328010, NP\_149016.1, HSM801092.at  
 Figure 7458: PRO83928  
 Figure 7459: DNA262805, DNA262805, HSM800425.at  
 Figure 7460: DNA331146, 1400830.1, HUMJNLTRA.at  
 Figure 7461: PRO86284  
 Figure 7462: DNA328317, cig5, AF026941.at  
 Figure 7463: PRO69493  
 Figure 7464: DNA331147, NP\_079104.1, AF131768.at  
 Figure 7465: PRO86285  
 Figure 7466: DNA255770, DNA255770, AK022106.at  
 Figure 7467A-C: DNA254412, EVI5, AF008915.at  
 Figure 7468: PRO49522  
 Figure 7469: DNA331148, 978273.10, AK023244.at  
 Figure 7470: PRO86286  
 Figure 7471: DNA330532, AK026279, AK026279.at  
 Figure 7472: PRO85719  
 Figure 7473: DNA330388, FLJ23468, AK027121.at  
 Figure 7474: PRO85597  
 Figure 7475: DNA331927, AK026969, AK026969.at  
 Figure 7476: PRO86807  
 Figure 7477: DNA330447, FLJ22757, AK026410.at  
 Figure 7478: PRO85648  
 Figure 7479: DNA324984, FLJ12298, AK022360.at  
 Figure 7480: PRO81578  
 Figure 7481: DNA331149, 7697327.1, HSM802839.at  
 Figure 7482: PRO86287  
 Figure 7483A-B: DNA256267, DNA256267, AK023113.at  
 Figure 7484: PRO51311  
 Figure 7485: DNA331150, BC017725, 1387341.2.at  
 Figure 7486: PRO86288  
 Figure 7487: DNA257606, DNA257606, 428093.1.at  
 Figure 7488: DNA258375, AF283301, 413231.5.at  
 Figure 7489: PRO52516  
 Figure 7490: DNA331928, AK027419, 154551.10.at  
 Figure 7491: PRO86808  
 Figure 7492: DNA328319, BC019562, 411364.2.at  
 Figure 7493: DNA290812, DNA290812, 220495.3.CON.at  
 Figure 7494: PRO70559  
 Figure 7495: DNA304799, BC022410, 337588.1.at  
 Figure 7496: PRO52633  
 Figure 7497: DNA257403, DNA257403, 012814.1.at  
 Figure 7498: DNA304820, NP\_115940.1, 317557.1.at  
 Figure 7499: PRO47351  
 Figure 7500: DNA331929, BC019246,

441855.8\_CON.at  
 Figure 7501: PRO83338  
 Figure 7502: DNA260581, DNA260581, 127987.6.at  
 Figure 7503: PRO54507  
 Figure 7504: DNA257576, DNA257576, 334945.2.at  
 Figure 7505: DNA304819, BC004398, 202113.2.at  
 Figure 7506: DNA304794, FBXO30, 222128.1.at  
 Figure 7507: PRO71206  
 Figure 7508: DNA259323, DNA259323, 022997.1.at  
 Figure 7509: PRO53256  
 Figure 7510: DNA304796, MED8, 237428.13.at  
 Figure 7511: PRO71208  
 Figure 7512: DNA259615, DNA259615, 1000203.1.at  
 Figure 7513: DNA304805, AK027628, 475113.7.at  
 Figure 7514: PRO69531  
 Figure 7515: DNA304793, GBP4, 206425.2.at  
 Figure 7516: PRO71205  
 Figure 7517: DNA331151, 018033.1, 018033.1\_CON.at  
 Figure 7518: PRO86289  
 Figure 7519: DNA304068, AK057631, 1091656.1.at  
 Figure 7520: PRO71035  
 Figure 7521: DNA257714, EPSTI1, 337352.17.at  
 Figure 7522: PRO52268  
 Figure 7523: DNA304798, NP\_443097.1, 246119.7.at  
 Figure 7524: PRO71210  
 Figure 7525: DNA258721, DNA258721, 197627.1.at  
 Figure 7526A-B: DNA257461, NP\_113607.1, 086533.1.at  
 Figure 7527: PRO52040  
 Figure 7528: DNA331152, 1042156.3, 1042156.3.at  
 Figure 7529: PRO86290  
 Figure 7530: DNA331153, 004052.1, 004052.1.at  
 Figure 7531: PRO86291  
 Figure 7532: DNA331930, AK054582, 978231.1.at  
 Figure 7533: PRO86809  
 Figure 7534: DNA259587, DNA259587, 220866.1.at  
 Figure 7535: DNA106195, DNA106195, 359193.13.at  
 Figure 7536: DNA331154, 212376.1, 212376.1.at  
 Figure 7537: PRO86292  
 Figure 7538: DNA331155, 112652.1, 112652.1.at  
 Figure 7539: PRO86293  
 Figure 7540: DNA304806, BC019022, 983343.1.at  
 Figure 7541: PRO71215  
 Figure 7542: DNA262708, DNA262708, 118516.1\_RC.at  
 Figure 7543: DNA259475, DNA259475, 239162.1.at  
 Figure 7544: DNA269148, DNA269148, 411192.2.at  
 Figure 7545: DNA304817, BC015532, 211436.3.at  
 Figure 7546: PRO71224  
 Figure 7547: DNA260313, DNA260313, 1098929.1.at  
 Figure 7548: PRO54242  
 Figure 7549A-B: DNA328325, NP\_061142.1, 445188.4.at  
 Figure 7550: PRO84190  
 Figure 7551A-B: DNA304800, SERPINB9, 354740.1.at  
 Figure 7552: PRO69458  
 Figure 7553: DNA331156, 118180.1, 118180.1.at  
 Figure 7554: PRO86294  
 Figure 7555: DNA287659, AK027790, 406833.1.at  
 Figure 7556: PRO69903  
 Figure 7557: DNA331931, 092555.3, 092555.4.at  
 Figure 7558: PRO86810  
 Figure 7559: DNA331157, NP\_439896.1, 022541.5.at  
 Figure 7560: PRO86295  
 Figure 7561: DNA260573, DNA260573, 899597.1.at  
 Figure 7562: PRO54499  
 Figure 7563: DNA260157, DNA260157, 236833.1.at  
 Figure 7564: PRO54086  
 Figure 7565: DNA174145, DNA174145, 100083.2.at  
 Figure 7566: PRO35770  
 Figure 7567: DNA260167, DNA260167, 264556.1.at  
 Figure 7568A-B: DNA331932, 239260.1, 239260.1.at  
 Figure 7569: PRO86811  
 Figure 7570: DNA260031, DNA260031, 161526.1.at  
 Figure 7571: DNA258907, DNA258907, 347940.2.at  
 Figure 7572: PRO52840  
 Figure 7573: DNA257455, DNA257455, 977723.3.at  
 Figure 7574: PRO52035  
 Figure 7575: DNA304807, BC014978, 005415.2.at  
 Figure 7576: PRO71216  
 Figure 7577: DNA258864, DNA258864, 331965.1.at  
 Figure 7578: DNA304811, 428051.2, 428051.2.at  
 Figure 7579: PRO71220  
 Figure 7580: DNA257389, FLJ14906, 987098.1.at  
 Figure 7581: PRO51974  
 Figure 7582: DNA331158, 130352.1, 130352.1.at  
 Figure 7583: PRO86296  
 Figure 7584: DNA258951, DNA258951, 222361.1.at  
 Figure 7585: DNA331159, NP\_077291.1, 411426.29.at  
 Figure 7586: PRO86297  
 Figure 7587: DNA257784, DNA257784, 481853.1.at  
 Figure 7588: DNA331933, AF272148, 074299.1.at  
 Figure 7589: PRO86812

### BRIEF DESCRIPTION OF THE DRAWINGS

In the list of figures for the present application, specific cDNA sequences which are differentially expressed in differentiated macrophages as compared to normal undifferentiated monocytes are individually identified with a specific alphanumerical designation. These cDNA sequences are differentially expressed in monocytes that are specifically treated as described in Example 1 below. If start and/or stop codons have been identified in a cDNA sequence shown in the attached figures, they are shown in bold and underlined font, and the encoded polypeptide is shown in the next consecutive figure.

The Figures 1-7589 show the nucleic acids of the invention and their encoded PRO polypeptides. Also included, for convenience is a List of Figures, which gives the figure number and the corresponding DNA or PRO number.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

#### I. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide

ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a

PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this

method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X," "Y" and "Z" each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % amino acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i.e., the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an the amino acid sequence A which has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the

length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code

for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides.

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic

acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the

specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

5 The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

10 Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, 15 in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody 20 compositions with polypeptidic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

25 "Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The 30 higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

35 "Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM 40 sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl,

0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

5 "Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium  
10 phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO  
15 polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10  
20 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is  
25 "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

30 "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to  
35 induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a  
40 biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules

specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN<sup>TM</sup>, polyethylene glycol (PEG), and PLURONICS<sup>TM</sup>.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies (Zapata et al., *Protein Eng.* 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')<sub>2</sub> fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V<sub>H</sub>-V<sub>L</sub> dimer. Collectively, the six CDRs confer antigen-

binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')<sub>2</sub> antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv" or "sFv" antibody fragments comprise the V<sub>H</sub> and V<sub>L</sub> domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V<sub>H</sub> and V<sub>L</sub> domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) in the same polypeptide chain (V<sub>H</sub>-V<sub>L</sub>). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

The term "immune related disease" means a disease in which a component of the immune system of a mammal causes, mediates or otherwise contributes to a morbidity in the mammal. Also included are diseases in which stimulation or intervention of the immune response has an ameliorative effect on progression of the disease. Included within this term are immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

The term "T cell mediated disease" means a disease in which T cells directly or indirectly mediate or otherwise contribute to a morbidity in a mammal. The T cell mediated disease may be associated with cell mediated effects, lymphokine mediated effects, *etc.*, and even effects associated with B cells if the B cells are stimulated, for example, by the lymphokines secreted by T cells.

Examples of immune-related and inflammatory diseases, some of which are immune or T cell mediated, which can be treated according to the invention include systemic lupus erythematosus, rheumatoid arthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis,

granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic  
5 diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease. Infectious diseases including viral diseases such as AIDS (HIV infection), hepatitis A, B, C, D, and E, herpes, *etc.*, bacterial infections, fungal infections, protozoal infections and parasitic infections.

The term "effective amount" is a concentration or amount of a PRO polypeptide and/or  
10 agonist/antagonist which results in achieving a particular stated purpose. An "effective amount" of a PRO polypeptide or agonist or antagonist thereof may be determined empirically. Furthermore, a "therapeutically effective amount" is a concentration or amount of a PRO polypeptide and/or agonist/antagonist which is effective for achieving a stated therapeutic effect. This amount may also be determined empirically.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function  
15 of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.*,  $I^{131}$ ,  $I^{125}$ ,  $Y^{90}$  and  $Re^{186}$ ), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include adriamycin, doxorubicin, epirubicin, 5-fluorouracil, cytosine arabinoside  
20 ("Ara-C"), cyclophosphamide, thiopeta, busulfan, cytoxan, taxoids, *e.g.*, paclitaxel (Taxol, Bristol-Myers Squibb Oncology, Princeton, NJ), and doxetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France), toxotere, methotrexate, cisplatin, melphalan, vinblastine, bleomycin, etoposide, ifosfamide, mitomycin C, mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), melphalan and other related nitrogen  
25 mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors such as tamoxifen and onapristone.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially cancer cell overexpressing any of the genes identified herein, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent is one which significantly reduces the percentage of cells  
30 overexpressing such genes in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine,  
35 mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in *The Molecular Basis of Cancer*, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami *et al.* (WB Saunders: Philadelphia, 1995), especially p. 13.

The term "cytokine" is a generic term for proteins released by one cell population which act on  
40 another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and

traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prolaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; 5 fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- $\alpha$  and - $\beta$ ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- $\beta$ ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- $\alpha$  and TGF- $\beta$ ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon- $\alpha$ , - $\beta$ , and - $\gamma$ ; colony stimulating factors (CSFs) such as 10 macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1 $\alpha$ , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- $\alpha$  or TNF- $\beta$ ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

15 As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (*i.e.*, is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin 20 molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

25 As used herein, the term "inflammatory cells" designates cells that enhance the inflammatory response such as mononuclear cells, eosinophils, macrophages, and polymorphonuclear neutrophils (PMN).

**Table 1**

```

/*
5  *
   * C-C increased from 12 to 15
   * Z is average of EQ
   * B is average of ND
   * match with stop is _M; stop-stop = 0; J (joker) match = 0
10 */
#define _M      -8      /* value of a match with a stop */

int _day[26][26]={
/*  A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
15 /* A */ { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
   /* B */ { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
   /* C */ {-2, -4, 15, -5, -5, -4, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
   /* D */ { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
   /* E */ { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
20 /* F */ {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
   /* G */ { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
   /* H */ {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
   /* I */ {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
   /* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
25 /* K */ {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
   /* L */ {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
   /* M */ {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
   /* N */ { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
   /* O */ {_M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, 0, _M, _M, _M, _M, _M, _M, _M, _M, _M},
30 /* P */ { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
   /* Q */ { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
   /* R */ {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, 3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
   /* S */ { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
   /* T */ { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
35 /* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
   /* V */ { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
   /* W */ {-6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
   /* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
   /* Y */ {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
40 /* Z */ { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

```

**Table 1 (cont')**

```

/*
*/
#include <stdio.h>
5  #include <ctype.h>

#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
10  #define MX        4      /* save if there's at least MX-1 bases since last jmp */

#define DMAT         3      /* value of matching bases */
#define DMIS         0      /* penalty for mismatched bases */
#define DINS0        8      /* penalty for a gap */
15  #define DINS1        1     /* penalty per base */
#define PINS0        8      /* penalty for a gap */
#define PINS1        4      /* penalty per residue */

struct jmp {
20      short          n[MAXJMP];      /* size of jmp (neg for dely) */
      unsigned short  x[MAXJMP];      /* base no. of jmp in seq x */
};                                     /* limits seq to 2^16 -1 */

struct diag {
25      int            score;           /* score at last jmp */
      long            offset;          /* offset of prev block */
      short           ijmp;            /* current jmp index */
      struct jmp      jp;              /* list of jmps */
30  };

struct path {
      int             spc;              /* number of leading spaces */
      short           n[JMPS];          /* size of jmp (gap) */
      int             x[JMPS];          /* loc of jmp (last elem before gap) */
35  };

char      *ofile;                      /* output file name */
char      *namex[2];                   /* seq names: getseqs() */
char      *prog;                       /* prog name for err msgs */
40  char      *seqx[2];                  /* seqs: getseqs() */
int        dmax;                       /* best diag: nw() */
int        dmax0;                      /* final diag */
int        dna;                        /* set if dna: main() */
int        endgaps;                    /* set if penalizing end gaps */
45  int        gapx, gapy;               /* total gaps in seqs */
int        len0, len1;                 /* seq lens */
int        ngapx, ngapy;               /* total size of gaps */
int        smax;                       /* max score: nw() */
int        *xbm;                       /* bitmap for matching */
50  long       offset;                   /* current offset in jmp file */
struct     diag      *dx;               /* holds diagonals */
struct     path      pp[2];             /* holds path for seqs */

char      *calloc(), *malloc(), *index(), *strcpy();
55  char      *getseq(), *g_calloc();

```

60

**Table 1 (cont')**

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
5  * where file1 and file2 are two dna or two protein sequences.
* The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
10 * Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
15 #include "nw.h"
#include "day.h"

static _dbval[26] = {
20 1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
25 1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
30 main
int ac;
char *av[ ];
{
35 prog = av[0];
if (ac != 3) {
printf(stderr, "usage: %s file1 file2\n", prog);
printf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
printf(stderr, "The sequences can be in upper- or lower-case\n");
printf(stderr, "Any lines beginning with ';', '>' or '<' are ignored\n");
40 printf(stderr, "Output is in the file \"align.out\"\n");
exit(1);
}
namex[0] = av[1];
namex[1] = av[2];
45 seqx[0] = getseq(namex[0], &len0);
seqx[1] = getseq(namex[1], &len1);
xbm = (dna)? _dbval : _pbval;

endgaps = 0; /* 1 to penalize endgaps */
50 ofile = "align.out"; /* output file */

nw(); /* fill in the matrix, get the possible jmps */
readjmps(); /* get the actual jmps */
print(); /* print stats, alignment */
55 cleanup(0); /* unlink any tmp files */
}
60

```

**Table 1 (cont')**

```

/* do the alignment, return best score: main()
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
5  * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw0
10  nw
{
    char      *px, *py;      /* seqs and ptrs */
    int       *ndely, *dely; /* keep track of dely */
    int       ndelx, delx;    /* keep track of delx */
15  int       *tmp;          /* for swapping row0, row1 */
    int       mis;           /* score for each type */
    int       ins0, ins1;     /* insertion penalties */
    register  id;            /* diagonal index */
    register  ij;            /* jmp index */
20  register  *col0, *col1;   /* score for curr, last row */
    register  xx, yy;        /* index into seqs */

    dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

25  ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
    dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
    col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
    col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
    ins0 = (dna)? DINS0 : PINS0;
30  ins1 = (dna)? DINS1 : PINS1;

    smax = -10000;
    if (endgaps) {
        for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
35             col0[yy] = dely[yy] = col0[yy-1] - ins1;
             ndely[yy] = yy;
        }
        col0[0] = 0;      /* Waterman Bull Math Biol 84 */
    }
40  else
        for (yy = 1; yy <= len1; yy++)
            dely[yy] = -ins0;

    /* fill in match matrix
    */
45  for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
        /* initialize first entry in col
        */
        if (endgaps) {
50             if (xx == 1)
                col1[0] = delx = -(ins0+ins1);
            else
                col1[0] = delx = col0[0] - ins1;
            ndelx = xx;
55         }
        else {
            col1[0] = 0;
            delx = -ins0;
            ndelx = 0;
60         }
    }

```

**Table 1 (cont')****...nw**

```

5      for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
        mis = col0[yy-1];
        if (dna)
            mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
        else
            mis += _day[*px-'A'][*py-'A'];

10      /* update penalty for del in x seq;
        * favor new del over ongong del
        * ignore MAXGAP if weighting endgaps
        */
        if (endgaps || ndely[yy] < MAXGAP) {
15            if (col0[yy] - ins0 >= dely[yy]) {
                dely[yy] = col0[yy] - (ins0+ins1);
                ndely[yy] = 1;
            } else {
                dely[yy] -= ins1;
                ndely[yy]++;
20            }
        } else {
            if (col0[yy] - (ins0+ins1) >= dely[yy]) {
25                dely[yy] = col0[yy] - (ins0+ins1);
                ndely[yy] = 1;
            } else
                ndely[yy]++;
        }

30      /* update penalty for del in y seq;
        * favor new del over ongong del
        */
        if (endgaps || ndelx < MAXGAP) {
35            if (col1[yy-1] - ins0 >= delx) {
                delx = col1[yy-1] - (ins0+ins1);
                ndelx = 1;
            } else {
                delx -= ins1;
                ndelx++;
40            }
        } else {
            if (col1[yy-1] - (ins0+ins1) >= delx) {
                delx = col1[yy-1] - (ins0+ins1);
                ndelx = 1;
45            } else
                ndelx++;
        }

50      /* pick the maximum score; we're favoring
        * mis over any del and delx over dely
        */

```

55

60

**Table 1 (cont')**

...nw

```

5      id = xx - yy + len1 - 1;
      if (mis >= delx && mis >= dely[yy])
          col1[yy] = mis;
      else if (delx >= dely[yy]) {
          col1[yy] = delx;
          ij = dx[id].ijmp;
          if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
              dx[id].ijmp++;
              if (++ij >= MAXJMP) {
                  writejmps(id);
                  ij = dx[id].ijmp = 0;
15      dx[id].offset = offset;
                  offset += sizeof(struct jmp) + sizeof(offset);
              }
          }
          dx[id].jp.n[ij] = ndelx;
          dx[id].jp.x[ij] = xx;
          dx[id].score = delx;
      }
      else {
          col1[yy] = dely[yy];
          ij = dx[id].ijmp;
25      if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
          && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
              dx[id].ijmp++;
              if (++ij >= MAXJMP) {
30      writejmps(id);
                  ij = dx[id].ijmp = 0;
                  dx[id].offset = offset;
                  offset += sizeof(struct jmp) + sizeof(offset);
              }
          }
          dx[id].jp.n[ij] = -ndely[yy];
          dx[id].jp.x[ij] = xx;
          dx[id].score = dely[yy];
      }
40      if (xx == len0 && yy < len1) {
          /* last col
          */
          if (endgaps)
              col1[yy] -= ins0+ins1*(len1-yy);
          if (col1[yy] > smax) {
45      smax = col1[yy];
              dmax = id;
          }
      }
50      }
      if (endgaps && xx < len0)
          col1[yy-1] -= ins0+ins1*(len0-xx);
      if (col1[yy-1] > smax) {
          smax = col1[yy-1];
55      dmax = id;
      }
      tmp = col0; col0 = col1; col1 = tmp;
  }
  (void) free((char *)ndely);
  (void) free((char *)dely);
  (void) free((char *)col0);
  (void) free((char *)col1);
}

```

**Table 1 (cont')**

```

/*
 *
 * print() -- only routine visible outside this module
5  *
 * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[ ]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
10 * nums() -- put out a number line: dumpblock()
 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */
15
#include "nw.h"

#define SPC      3
#define P_LINE  256      /* maximum output line */
20 #define P_SPC   3        /* space between name or num and seq */

extern _day[26][26];
int olen;                /* set output line length */
FILE *fx;                /* output file */
25

print()

    print
    {
30        int    lx, ly, firstgap, lastgap;        /* overlap */

        if ((fx = fopen(ofile, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, ofile);
            cleanup(1);
        }
35        fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
        fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
        olen = 60;
        lx = len0;
        ly = len1;
40        firstgap = lastgap = 0;
        if (dmax < len1 - 1) {                /* leading gap in x */
            pp[0].spc = firstgap = len1 - dmax - 1;
            ly -= pp[0].spc;
        }
45        else if (dmax > len1 - 1) {          /* leading gap in y */
            pp[1].spc = firstgap = dmax - (len1 - 1);
            lx -= pp[1].spc;
        }
        if (dmax0 < len0 - 1) {                /* trailing gap in x */
50            lastgap = len0 - dmax0 - 1;
            lx -= lastgap;
        }
        else if (dmax0 > len0 - 1) {          /* trailing gap in y */
55            lastgap = dmax0 - (len0 - 1);
            ly -= lastgap;
        }
        getmat(lx, ly, firstgap, lastgap);
        pr_align();
60    }

```

**Table 1 (cont')**

```

/*
 * trace back the best path, count matches
 */
5 static
  getmat(lx, ly, firstgap, lastgap)                                getmat
  {
    int      lx, ly;                                           /* "core" (minus endgaps) */
    int      firstgap, lastgap;                                /* leading trailing overlap */

10    int      nm, i0, i1, siz0, siz1;
    char      outx[32];
    double    pct;
    register  n0, n1;
    register char *p0, *p1;

15    /* get total matches, score
    */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
    n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;

20    nm = 0;
    while ( *p0 && *p1 ) {
      if (siz0) {
        p1++;
        n1++;
        siz0--;

30      }
      else if (siz1) {
        p0++;
        n0++;
        siz1--;

35      }
      else {
        if (xbm[*p0-'A'] & xbm[*p1-'A'])
          nm++;
        if (n0++ == pp[0].x[i0])
          siz0 = pp[0].n[i0++];
        if (n1++ == pp[1].x[i1])
          siz1 = pp[1].n[i1++];
        p0++;
        p1++;

40      }
    }

45    }

    /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
    */
    if (endgaps)
      lx = (len0 < len1)? len0 : len1;
    else
      lx = (lx < ly)? lx : ly;

50    pct = 100.*((double)nm)/((double)lx);
    fprintf(fx, "\n");
    fprintf(fx, "<%d match%s in an overlap of %d: %.2f percent similarity\n",
      nm, (nm == 1)? "" : "es", lx, pct);

60

```

**Table 1 (cont')**

```

5      fprintf(fx, "<gaps in first sequence: %d", gapx);
      if (gapx) {
          (void) sprintf(outx, " (%d %s%s)",
              ngapx, (dna)? "base":"residue", (ngapx == 1)? "" : "s");
          fprintf(fx, "%s", outx);

10     fprintf(fx, ", gaps in second sequence: %d", gapy);
      if (gapy) {
          (void) sprintf(outx, " (%d %s%s)",
              ngapy, (dna)? "base":"residue", (ngapy == 1)? "" : "s");
          fprintf(fx, "%s", outx);

15     }
      if (dna)
          fprintf(fx,
              "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
              smax, DMAT, DMIS, DINS0, DINS1);
      else
20     fprintf(fx,
              "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
              smax, PINS0, PINS1);
      if (endgaps)
          fprintf(fx,
25     "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
              firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
              lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
      else
          fprintf(fx, "<endgaps not penalized\n");

30 }
      static      nm;          /* matches in core -- for checking */
      static      lmax;        /* lengths of stripped file names */
      static      ij[2];       /* jmp index for a path */
      static      nc[2];       /* number at start of current line */
35     static      ni[2];       /* current elem number -- for gapping */
      static      siz[2];
      static char  *ps[2];      /* ptr to current element */
      static char  *po[2];      /* ptr to next output char slot */
      static char  out[2][P_LINE]; /* output line */
40     static char  star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp[ ]
 */
45     static
pr_align()
{
    int      nn;      /* char count */
    int      more;
50     register  i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(namex[i]);
        if (nn > lmax)
55             lmax = nn;

        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
60     ps[i] = seqx[i];
        po[i] = out[i];
    }

```

...getmat

pr\_align

**Table 1 (cont')****...pr\_align**

```

5      for (nn = nm = 0, more = 1; more;) {
        for (i = more = 0; i < 2; i++) {
            /*
            * do we have more of this sequence?
            */
            if (!*ps[i])
10                continue;

                more++;

            if (pp[i].spc) { /* leading space */
                *po[i]++ = ' ';
                pp[i].spc--;
15            }
            else if (siz[i]) { /* in a gap */
                *po[i]++ = '-';
                siz[i]--;
20            }
            else { /* we're putting a seq element
                    */
                *po[i] = *ps[i];
                if (islower(*ps[i]))
25                    *ps[i] = toupper(*ps[i]);
                po[i]++;
                ps[i]++;

                /*
                * are we at next gap for this seq?
                */
                if (ni[i] == pp[i].x[ij[i]]) {
                    /*
                    * we need to merge all gaps
                    * at this location
                    */
                    siz[i] = pp[i].n[ij[i]++];
                    while (ni[i] == pp[i].x[ij[i]])
40                        siz[i] += pp[i].n[ij[i]++];
                }
                ni[i]++;
            }
        }
        if (++nn == olen || !more && nn) {
45            dumpblock();
            for (i = 0; i < 2; i++)
                po[i] = out[i];
            nn = 0;
        }
50    }
}

/*
* dump a block of lines, including numbers, stars: pr_align()
55 */
static
dumpblock()
    dumpblock
{
60    register i;
    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';

```

**Table 1 (cont')****...dumpblock**

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (i == 0)
                  nums(i);
              if (i == 0 && *out[1])
10                 stars();
              putline(i);
              if (i == 0 && *out[1])
                  fprintf(fx, star);
              if (i == 1)
15                 nums(i);
          }
      }
  }

20  /*
   * put out a number line: dumpblock()
   */
   static
   nums(ix)
25  {
      int      ix;      /* index in out[ ] holding seq line */

      char      nline[P_LINE];
      register  i, j;
      register char *pn, *px, *py;
30
      for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
          *pn = ' ';
      for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
          if (*py == ' ' || *py == '-')
35             *pn = ' ';
          else {
              if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                  j = (i < 0)? -i : i;
                  for (px = pn; j; j /= 10, px--)
40                     *px = j%10 + '0';
                  if (i < 0)
                      *px = '-';
              }
              else
45                 *pn = ' ';
              i++;
          }
      }
      *pn = '\0';
      nc[ix] = i;
      for (pn = nline; *pn; pn++)
          (void) putc(*pn, fx);
      (void) putc('\n', fx);
55  }

  /*
   * put out a line (name, [num], seq, [num]): dumpblock()
   */
   static
60  putline(ix)
      int      ix;
      {

```

**nums****putline**

**Table 1 (cont')**

...putline

```

5      int          i;
      register char *px;

      for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
          (void) putc(*px, fx);
10     for (; i < lmax+P_SPC; i++)
          (void) putc(' ', fx);

      /* these count from 1:
      * ni[ ] is current element (from 1)
      * nc[ ] is number at start of current line
      */
15     for (px = out[ix]; *px; px++)
          (void) putc(*px&0x7F, fx);
      (void) putc('\n', fx);
20 }

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock()
 */
25 static
stars()
{
    stars
    {
30         int          i;
        register char *p0, *p1, cx, *px;

        if (!*out[0] || (*out[0] == '' && *(po[0] == '' ||
            !*out[1] || (*out[1] == '' && *(po[1] == '' ))
            return;
35         px = star;
        for (i = lmax+P_SPC; i; i--)
            *px++ = ' ';

        for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
40             if (isalpha(*p0) && isalpha(*p1)) {

                    if (xbm[*p0-'A']&xbm[*p1-'A']) {
                            cx = '*';
                            nm++;
45                     }
                    else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                            cx = ':';
                    else
                            cx = ' ';
50             }
            else
                    cx = ' ';
            *px++ = cx;
        }
55     *px++ = '\n';
    *px = '\0';
}
60

```

**Table 1 (cont')**

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
5 static
  stripname(pn)
      stripname
      char    *pn;    /* file name (may be path) */
10 {
      register char    *px, *py;

      py = 0;
      for (px = pn; *px; px++)
          if (*px == '/')
15              py = px + 1;
      if (py)
          (void) strcpy(pn, py);
      return(strlen(pn));
20 }

25

30

35

40

45

50

55

60
```

**Table 1 (cont')**

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
5  * g_calloc() -- calloc() with error checkin
 * readjumps() -- get the good jumps, from tmp file if necessary
 * writejumps() -- write a filled array of jumps to a tmp file: nw()
 */
10 #include "nw.h"
#include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";          /* tmp file for jumps */
FILE    *fj;

15 int    cleanup();                          /* cleanup tmp file */
long    lseek();

/*
 * remove any tmp file if we blow
20 */
cleanup(i)
    int    i;
{
    if (fj)
25         (void) unlink(jname);
    exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
30 char    *
getseq(file, len)
35     char    *file;    /* file name */
    int    *len;    /* seq len */
{
    char    line[1024], *pseq;
40     register char    *px, *py;
    int    natgc, tlen;
    FILE    *fp;

    if ((fp = fopen(file, "r")) == 0) {
45         fprintf(stderr, "%s: can't read %s\n", prog, file);
        exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
50         if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
55     }
    if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
        fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
60     pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

**Table 1 (cont')**

...getseq

```

5      py = pseq + 4;
      *len = tlen;
      rewind(fp);

      while (fgets(line, 1024, fp)) {
          if (*line == ';' || *line == '<' || *line == '>')
              continue;
10         for (px = line; *px != '\n'; px++) {
              if (isupper(*px))
                  *py++ = *px;
              else if (islower(*px))
                  *py++ = toupper(*px);
15             if (index("ATGCU", *(py-1)))
                  natgc++;
          }
      }
      *py++ = '\0';
      *py = '\0';
      (void) fclose(fp);
      dna = natgc > (tlen/3);
      return(pseq+4);
25 }

char *
g_alloc(msg, nx, sz)
char *msg;          /* program, calling routine */
int nx, sz;          /* number and size of elements */
30 {
    char *px, *calloc;

    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
35             fprintf(stderr, "%s: g_alloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
40 }

/*
 * get final jmps from dx[ ] or tmp file, set pp[ ], reset dmax: main()
 */
45 readjmps()
    readjmps
{
    int fd = -1;
    int siz, i0, i1;
50 register i, j, xx;

    if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
55             fprintf(stderr, "%s: can't open() %s\n", prog, jname);
            cleanup(1);
        }
    }
    for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
60         while (1) {
            for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                ;

```

g\_alloc

**Table 1 (cont')****...readjumps**

```

5         if (j < 0 && dx[dmax].offset && fj) {
            (void) lseek(fd, dx[dmax].offset, 0);
            (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
            (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
            dx[dmax].ijmp = MAXJMP-1;
        }
10        else
            break;
    }
    if (i >= JMPS) {
        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
        cleanup(1);
15    }
    if (j >= 0) {
        siz = dx[dmax].jp.n[j];
        xx = dx[dmax].jp.x[j];
        dmax += siz;
20        if (siz < 0) { /* gap in second seq */
            pp[1].n[i1] = -siz;
            xx += siz;
            /* id = xx - yy + len1 - 1
            */
            pp[1].x[i1] = xx - dmax + len1 - 1;
            gapy++;
            ngapy -= siz;
/* ignore MAXGAP when doing endgaps */
            siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
30            i1++;
        }
        else if (siz > 0) { /* gap in first seq */
            pp[0].n[i0] = siz;
            pp[0].x[i0] = xx;
            gapx++;
            ngapx += siz;
/* ignore MAXGAP when doing endgaps */
            siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
40            i0++;
        }
    }
    else
        break;
}

45 /* reverse the order of jumps
*/
for (j = 0, i0--; j < i0; j++, i0--) {
    i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
50    i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
}
for (j = 0, i1--; j < i1; j++, i1--) {
    i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
    i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
55 }
if (fd >= 0)
    (void) close(fd);
if (fj) {
    (void) unlink(jname);
60    fj = 0;
    offset = 0;
}
}

```

**Table 1 (cont')**

```

5  /*
   * write a filled jmp struct offset of the prev one (if any): nw()
   */
   writejumps(ix)
       writejumps
           int      ix;
10  {
           char      *mktemp();

           if (!fj) {
               if (mktemp(jname) < 0) {
                   fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                   cleanup(1);
15               }
               if ((fj = fopen(jname, "w")) == 0) {
                   fprintf(stderr, "%s: can't write %s\n", prog, jname);
                   exit(1);
20               }
           }
           (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
           (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
           }
25

```

**Table 2**

5 PRO XXXXXXXXXXXXXXXX (Length = 15 amino acids)  
 Comparison Protein XXXXXYYYYYYY (Length = 12 amino acids)  
 % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as  
 10 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =  
 5 divided by 15 = 33.3%

**Table 3**

15 PRO XXXXXXXXXX (Length = 10 amino acids)  
 Comparison Protein XXXXXYYYYYYZZYZ (Length = 15 amino acids)  
 % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as  
 20 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =  
 5 divided by 10 = 50%

**Table 4**

25 PRO-DNA NNNNNNNNNNNNNN (Length = 14 nucleotides)  
 Comparison DNA NNNNNLLLLLLLLLLL (Length = 16 nucleotides)

% nucleic acid sequence identity =

30 (the number of identically matching nucleotides between the two nucleic acid sequences as determined by  
 ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =  
 6 divided by 14 = 42.9%

**Table 5**

35 PRO-DNA NNNNNNNNNNNN (Length = 12 nucleotides)  
 Comparison DNA NNNNLLLVV (Length = 9 nucleotides)

% nucleic acid sequence identity =

40

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) = 4 divided by 12 = 33.3%

## II. Compositions and Methods of the Invention

### A. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been disclosed. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

### B. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally, the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native

protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

	<u>Original Residue</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
20	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
25	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe;	
30		norleucine	leu
	Leu (L)	norleucine; ile; val;	
		met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
35	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
40	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe;	
		ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

- (2) neutral hydrophilic: cys, ser, thr;  
(3) acidic: asp, glu;  
(4) basic: asn, gln, his, lys, arg;  
(5) residues that influence chain orientation: gly, pro; and  
5 (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., **13**:4331 (1986); Zoller et al., Nucl. Acids Res., **10**:6487 (1987)], cassette mutagenesis [Wells et al., Gene, **34**:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, **317**:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

15 Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, **244**: 1081-1085 (1989)].  
20 Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., **150**:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

### C. Modifications of PRO

25 Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa.  
30 Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparaginy residues to the  
35 corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the  $\alpha$ -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al.,

Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an alpha-tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

#### D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

##### 1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., *supra*; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives

are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like  $^{32}\text{P}$ -labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

## 2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example,  $\text{CaCl}_2$ ,  $\text{CaPO}_4$ , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli*

strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescens*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan<sup>r</sup>*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan<sup>r</sup>*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylophilic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylophilic Yeasts, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC

CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen. Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

### 3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces*  $\alpha$ -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 $\mu$  plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR

activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the  $\beta$ -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the *tac* promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin,  $\alpha$ -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

#### 4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

#### 5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

### E. Tissue Distribution

The location of tissues expressing the PRO can be identified by determining mRNA expression in various human tissues. The location of such genes provides information about which tissues are most likely to be affected by the stimulating and inhibiting activities of the PRO polypeptides. The location of a gene in a specific tissue also provides sample tissue for the activity blocking assays discussed below.

As noted before, gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, *Proc. Natl. Acad. Sci. USA*, 77:5201-5205 [1980]), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence of a PRO polypeptide or against a synthetic peptide based on the DNA sequences encoding the PRO polypeptide or against an exogenous sequence fused to a DNA encoding a PRO polypeptide and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for Northern blotting and *in situ* hybridization are provided below.

### F. Antibody Binding Studies

The activity of the PRO polypeptides can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides, respectively, on tissue cells is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies, the preparation of which will be described hereinbelow.

Antibody binding studies may be carried out in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, *Monoclonal Antibodies: A Manual of Techniques*, pp.147-158 (CRC Press, Inc., 1987).

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies preferably are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte which remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody which is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. See, *e.g.*, US Pat No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using

an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

5           G.     Cell-Based Assays

Cell-based assays and animal models for immune related diseases can be used to further understand the relationship between the genes and polypeptides identified herein and the development and pathogenesis of immune related disease.

10           In a different approach, cells of a cell type known to be involved in a particular immune related disease are transfected with the cDNAs described herein, and the ability of these cDNAs to stimulate or inhibit immune function is analyzed. Suitable cells can be transfected with the desired gene, and monitored for immune function activity. Such transfected cell lines can then be used to test the ability of poly- or monoclonal antibodies or antibody compositions to inhibit or stimulate immune function, for example to modulate T-cell proliferation or inflammatory cell infiltration. Cells transfected with the coding sequences  
15 of the genes identified herein can further be used to identify drug candidates for the treatment of immune related diseases.

20           In addition, primary cultures derived from transgenic animals (as described below) can be used in the cell-based assays herein, although stable cell lines are preferred. Techniques to derive continuous cell lines from transgenic animals are well known in the art (see, *e.g.*, Small *et al.*, *Mol. Cell. Biol.* 5: 642-648 [1985]).

25           One suitable cell based assay is the mixed lymphocyte reaction (MLR). *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. In this assay, the ability of a test compound to stimulate or inhibit the proliferation of activated T cells is assayed. A suspension of responder T cells is cultured with allogeneic stimulator cells and the proliferation of T cells is measured by uptake of tritiated thymidine. This assay is a general measure of T cell reactivity. Since the majority of T cells respond to and produce IL-2 upon activation, differences in responsiveness in this assay in part reflect differences in IL-2 production by the responding cells. The MLR results can be verified by a standard lymphokine (IL-2) detection assay. *Current Protocols in Immunology*, above, 3.15, 6.3.

30           A proliferative T cell response in an MLR assay may be due to direct mitogenic properties of an assayed molecule or to external antigen induced activation. Additional verification of the T cell stimulatory activity of the PRO polypeptides can be obtained by a costimulation assay. T cell activation requires an antigen specific signal mediated through the T-cell receptor (TCR) and a costimulatory signal mediated through a second ligand binding interaction, for example, the B7 (CD80, CD86)/CD28 binding interaction.  
35 CD28 crosslinking increases lymphokine secretion by activated T cells. T cell activation has both negative and positive controls through the binding of ligands which have a negative or positive effect. CD28 and CTLA-4 are related glycoproteins in the Ig superfamily which bind to B7. CD28 binding to B7 has a positive costimulation effect of T cell activation; conversely, CTLA-4 binding to B7 has a T cell deactivating effect. Chambers, C. A. and Allison, J. P., *Curr. Opin. Immunol.* (1997) 9:396. Schwartz, R. H., *Cell* (1992) 71:1065; Linsey, P. S. and Ledbetter, J. A., *Annu. Rev. Immunol.* (1993) 11:191; June, C. H.  
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*et al, Immunol. Today* (1994) 15:321; Jenkins, M. K., *Immunity* (1994) 1:405. In a costimulation assay, the PRO polypeptides are assayed for T cell costimulatory or inhibitory activity.

Direct use of a stimulating compound as in the invention has been validated in experiments with 4-1BB glycoprotein, a member of the tumor necrosis factor receptor family, which binds to a ligand (4-1BBL) expressed on primed T cells and signals T cell activation and growth. Alderson, M. E. *et al., J. Immunol.* (1994) 24:2219.

The use of an agonist stimulating compound has also been validated experimentally. Activation of 4-1BB by treatment with an agonist anti-4-1BB antibody enhances eradication of tumors. Hellstrom, I. and Hellstrom, K. E., *Crit. Rev. Immunol.* (1998) 18:1. Immunoadjuvant therapy for treatment of tumors, described in more detail below, is another example of the use of the stimulating compounds of the invention.

Alternatively, an immune stimulating or enhancing effect can also be achieved by administration of a PRO which has vascular permeability enhancing properties. Enhanced vascular permeability would be beneficial to disorders which can be attenuated by local infiltration of immune cells (*e.g.*, monocytes, eosinophils, PMNs) and inflammation.

On the other hand, PRO polypeptides, as well as other compounds of the invention, which are direct inhibitors of T cell proliferation/activation, lymphokine secretion, and/or vascular permeability can be directly used to suppress the immune response. These compounds are useful to reduce the degree of the immune response and to treat immune related diseases characterized by a hyperactive, superoptimal, or autoimmune response. This use of the compounds of the invention has been validated by the experiments described above in which CTLA-4 binding to receptor B7 deactivates T cells. The direct inhibitory compounds of the invention function in an analogous manner. The use of compound which suppress vascular permeability would be expected to reduce inflammation. Such uses would be beneficial in treating conditions associated with excessive inflammation.

Alternatively, compounds, *e.g.*, antibodies, which bind to stimulating PRO polypeptides and block the stimulating effect of these molecules produce a net inhibitory effect and can be used to suppress the T cell mediated immune response by inhibiting T cell proliferation/activation and/or lymphokine secretion. Blocking the stimulating effect of the polypeptides suppresses the immune response of the mammal. This use has been validated in experiments using an anti-IL2 antibody. In these experiments, the antibody binds to IL2 and blocks binding of IL2 to its receptor thereby achieving a T cell inhibitory effect.

#### H. Animal Models

The results of the cell based *in vitro* assays can be further verified using *in vivo* animal models and assays for T-cell function. A variety of well known animal models can be used to further understand the role of the genes identified herein in the development and pathogenesis of immune related disease, and to test the efficacy of candidate therapeutic agents, including antibodies, and other antagonists of the native polypeptides, including small molecule antagonists. The *in vivo* nature of such models makes them predictive of responses in human patients. Animal models of immune related diseases include both non-recombinant and recombinant (transgenic) animals. Non-recombinant animal models include, for example, rodent, *e.g.*, murine models. Such models can be generated by introducing cells into syngeneic mice using

standard techniques, *e.g.*, subcutaneous injection, tail vein injection, spleen implantation, intraperitoneal implantation, implantation under the renal capsule, *etc.*

Graft-versus-host disease occurs when immunocompetent cells are transplanted into immunosuppressed or tolerant patients. The donor cells recognize and respond to host antigens. The response can vary from life threatening severe inflammation to mild cases of diarrhea and weight loss. Graft-versus-host disease models provide a means of assessing T cell reactivity against MHC antigens and minor transplant antigens. A suitable procedure is described in detail in *Current Protocols in Immunology*, above, unit 4.3.

An animal model for skin allograft rejection is a means of testing the ability of T cells to mediate *in vivo* tissue destruction and a measure of their role in transplant rejection. The most common and accepted models use murine tail-skin grafts. Repeated experiments have shown that skin allograft rejection is mediated by T cells, helper T cells and killer-effector T cells, and not antibodies. Auchincloss, H. Jr. and Sachs, D. H., *Fundamental Immunology*, 2nd ed., W. E. Paul ed., Raven Press, NY, 1989, 889-992. A suitable procedure is described in detail in *Current Protocols in Immunology*, above, unit 4.4. Other transplant rejection models which can be used to test the compounds of the invention are the allogeneic heart transplant models described by Tanabe, M. *et al*, *Transplantation* (1994) 58:23 and Tinubu, S. A. *et al*, *J. Immunol.* (1994) 4330-4338.

Animal models for delayed type hypersensitivity provides an assay of cell mediated immune function as well. Delayed type hypersensitivity reactions are a T cell mediated *in vivo* immune response characterized by inflammation which does not reach a peak until after a period of time has elapsed after challenge with an antigen. These reactions also occur in tissue specific autoimmune diseases such as multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE, a model for MS). A suitable procedure is described in detail in *Current Protocols in Immunology*, above, unit 4.5.

EAE is a T cell mediated autoimmune disease characterized by T cell and mononuclear cell inflammation and subsequent demyelination of axons in the central nervous system. EAE is generally considered to be a relevant animal model for MS in humans. Bolton, C., *Multiple Sclerosis* (1995) 1:143. Both acute and relapsing-remitting models have been developed. The compounds of the invention can be tested for T cell stimulatory or inhibitory activity against immune mediated demyelinating disease using the protocol described in *Current Protocols in Immunology*, above, units 15.1 and 15.2. See also the models for myelin disease in which oligodendrocytes or Schwann cells are grafted into the central nervous system as described in Duncan, I. D. *et al*, *Molec. Med. Today* (1997) 554-561.

Contact hypersensitivity is a simple delayed type hypersensitivity *in vivo* assay of cell mediated immune function. In this procedure, cutaneous exposure to exogenous haptens which gives rise to a delayed type hypersensitivity reaction which is measured and quantitated. Contact sensitivity involves an initial sensitizing phase followed by an elicitation phase. The elicitation phase occurs when the T lymphocytes encounter an antigen to which they have had previous contact. Swelling and inflammation occur, making this an excellent model of human allergic contact dermatitis. A suitable procedure is described in detail in *Current Protocols in Immunology*, Eds. J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, John Wiley & Sons, Inc., 1994, unit 4.2. See also Grabbe, S. and Schwarz, T, *Immun. Today* 19 (1): 37-44 (1998).

An animal model for arthritis is collagen-induced arthritis. This model shares clinical, histological and immunological characteristics of human autoimmune rheumatoid arthritis and is an acceptable model for human autoimmune arthritis. Mouse and rat models are characterized by synovitis, erosion of cartilage and subchondral bone. The compounds of the invention can be tested for activity against autoimmune arthritis using the protocols described in *Current Protocols in Immunology*, above, units 15.5. See also the model using a monoclonal antibody to CD18 and VLA-4 integrins described in Issekutz, A.C. *et al.*, *Immunology* (1996) 88:569.

A model of asthma has been described in which antigen-induced airway hyper-reactivity, pulmonary eosinophilia and inflammation are induced by sensitizing an animal with ovalbumin and then challenging the animal with the same protein delivered by aerosol. Several animal models (guinea pig, rat, non-human primate) show symptoms similar to atopic asthma in humans upon challenge with aerosol antigens. Murine models have many of the features of human asthma. Suitable procedures to test the compounds of the invention for activity and effectiveness in the treatment of asthma are described by Wolyniec, W. W. *et al.*, *Am. J. Respir. Cell Mol. Biol.* (1998) 18:777 and the references cited therein.

Additionally, the compounds of the invention can be tested on animal models for psoriasis like diseases. Evidence suggests a T cell pathogenesis for psoriasis. The compounds of the invention can be tested in the scid/scid mouse model described by Schon, M. P. *et al.*, *Nat. Med.* (1997) 3:183, in which the mice demonstrate histopathologic skin lesions resembling psoriasis. Another suitable model is the human skin/scid mouse chimera prepared as described by Nickoloff, B. J. *et al.*, *Am. J. Path.* (1995) 146:580.

Recombinant (transgenic) animal models can be engineered by introducing the coding portion of the genes identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (Hoppe and Wanger, U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, *Proc. Natl. Acad. Sci. USA* 82, 6148-615 [1985]); gene targeting in embryonic stem cells (Thompson *et al.*, *Cell* 56, 313-321 [1989]); electroporation of embryos (Lo, *Mol. Cel. Biol.* 3, 1803-1814 [1983]); sperm-mediated gene transfer (Lavitrano *et al.*, *Cell* 57, 717-73 [1989]). For review, see, for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in concatamers, *e.g.*, head-to-head or head-to-tail tandems. Selective introduction of a transgene into a particular cell type is also possible by following, for example, the technique of Lasko *et al.*, *Proc. Natl. Acad. Sci. USA* 89, 6232-636 (1992).

The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ* hybridization, Northern blot analysis, PCR, or immunocytochemistry.

The animals may be further examined for signs of immune disease pathology, for example by histological examination to determine infiltration of immune cells into specific tissues. Blocking

experiments can also be performed in which the transgenic animals are treated with the compounds of the invention to determine the extent of the T cell proliferation stimulation or inhibition of the compounds. In these experiments, blocking antibodies which bind to the PRO polypeptide, prepared as described above, are administered to the animal and the effect on immune function is determined.

Alternatively, "knock out" animals can be constructed which have a defective or altered gene encoding a polypeptide identified herein, as a result of homologous recombination between the endogenous gene encoding the polypeptide and altered genomic DNA encoding the same polypeptide introduced into an embryonic cell of the animal. For example, cDNA encoding a particular polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see *e.g.*, Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see *e.g.*, Li *et al.*, *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse or rat) to form aggregation chimeras [see *e.g.*, Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the polypeptide.

#### I. ImmunoAdjuvant Therapy

In one embodiment, the immunostimulating compounds of the invention can be used in immunoadjuvant therapy for the treatment of tumors (cancer). It is now well established that T cells recognize human tumor specific antigens. One group of tumor antigens, encoded by the MAGE, BAGE and GAGE families of genes, are silent in all adult normal tissues, but are expressed in significant amounts in tumors, such as melanomas, lung tumors, head and neck tumors, and bladder carcinomas. DeSmet, C. *et al.*, (1996) *Proc. Natl. Acad. Sci. USA*, 93:7149. It has been shown that costimulation of T cells induces tumor regression and an antitumor response both *in vitro* and *in vivo*. Melero, I. *et al.*, *Nature Medicine* (1997) 3:682; Kwon, E. D. *et al.*, *Proc. Natl. Acad. Sci. USA* (1997) 94: 8099; Lynch, D. H. *et al.*, *Nature Medicine* (1997) 3:625; Finn, O. J. and Lotze, M. T., *J. Immunol.* (1998) 21:114. The stimulatory compounds of the invention can be administered as adjuvants, alone or together with a growth regulating agent, cytotoxic agent or chemotherapeutic agent, to stimulate T cell proliferation/activation and an antitumor response to tumor antigens. The growth regulating, cytotoxic, or chemotherapeutic agent may be administered in conventional amounts using known administration regimes. Immunostimulating activity by the compounds of the invention allows reduced amounts of the growth regulating, cytotoxic, or chemotherapeutic agents thereby potentially lowering the toxicity to the patient.

#### J. Screening Assays for Drug Candidates

Screening assays for drug candidates are designed to identify compounds that bind to or complex with the polypeptides encoded by the genes identified herein or a biologically active fragment thereof, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds, including peptides, preferably soluble peptides, (poly)peptide-immunoglobulin fusions, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art. All assays are common in that they call for contacting the drug candidate with a polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labelled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular protein encoded by a gene identified herein, its interaction with that protein can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers [Fields and Song, *Nature (London)* 340, 245-246 (1989); Chien *et al.*, *Proc. Natl. Acad. Sci. USA* 88, 9578-9582 (1991)] as disclosed by Chevray and Nathans, *Proc. Natl. Acad. Sci. USA* 89, 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, while the other one functioning as the transcription activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate

activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for  $\beta$ -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two  
5 specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

In order to find compounds that interfere with the interaction of a gene identified herein and other intra- or extracellular components can be tested, a reaction mixture is usually prepared containing the  
10 product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a test compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described above.  
15 The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

#### K. Compositions and Methods for the Treatment of Immune Related Diseases

The compositions useful in the treatment of immune related diseases include, without limitation,  
20 proteins, antibodies, small organic molecules, peptides, phosphopeptides, antisense and ribozyme molecules, triple helix molecules, *etc.* that inhibit or stimulate immune function, for example, T cell proliferation/activation, lymphokine release, or immune cell infiltration.

For example, antisense RNA and RNA molecules act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. When antisense DNA is used,  
25 oligodeoxyribonucleotides derived from the translation initiation site, *e.g.*, between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified  
30 by known techniques. For further details see, *e.g.*, Rossi, *Current Biology* 4, 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple helix formation via Hoogsteen base pairing rules, which generally require  
35 sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, *e.g.*, PCT publication No. WO 97/33551, *supra*.

These molecules can be identified by any or any combination of the screening assays discussed above and/or by any other screening techniques well known for those skilled in the art.

## L. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

### 1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections.

The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

### 2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al.,

Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., supra] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

*In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

### 3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub> or other antigen-binding  
 5 subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by  
 10 corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The  
 15 humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These  
 20 non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeven et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric  
 25 antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage  
 30 display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous  
 35 immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology 10, 779-783 (1992); Lonberg *et al.*, Nature 368 856-859 (1994);

Morrison, Nature 368, 812-13 (1994); Fishwild *et al.*, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or human) from which the matured antibody is prepared.

#### 4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions.

It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh *et al.*, Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')<sub>2</sub> bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared can be prepared using

chemical linkage. Brennan *et al.*, Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby *et al.*, J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V<sub>H</sub> and V<sub>L</sub> domains of one fragment are forced to pair with the complementary V<sub>L</sub> and V<sub>H</sub> domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994). Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, J. Immunol. 147:60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

#### 5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been

proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

#### 6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, *J. Exp. Med.*, 176: 1191-1195 (1992) and Shopes, *J. Immunol.*, 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.*, *Cancer Research*, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, *Anti-Cancer Drug Design*, 3: 219-230 (1989).

#### 7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include  $^{212}\text{Bi}$ ,  $^{131}\text{I}$ ,  $^{131}\text{In}$ ,  $^{90}\text{Y}$ , and  $^{186}\text{Re}$ .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis-(p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, *Science*, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminopentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., **257**: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, J. National Cancer Inst., **81**(19): 1484 (1989).

M. Pharmaceutical Compositions

The active PRO molecules of the invention (*e.g.*, PRO polypeptides, anti-PRO antibodies, and/or variants of each) as well as other molecules identified by the screening assays disclosed above, can be administered for the treatment of immune related diseases, in the form of pharmaceutical compositions.

Therapeutic formulations of the active PRO molecule, preferably a polypeptide or antibody of the invention, are prepared for storage by mixing the active molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. [1980]), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN<sup>TM</sup>, PLURONICS<sup>TM</sup> or polyethylene glycol (PEG).

Compounds identified by the screening assays disclosed herein can be formulated in an analogous manner, using standard techniques well known in the art.

Lipofections or liposomes can also be used to deliver the PRO molecule into cells. Where antibody fragments are used, the smallest inhibitory fragment which specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable region sequences of an antibody, peptide molecules can be designed which retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology (see, e.g., Marasco *et al.*, *Proc. Natl. Acad. Sci. USA* 90, 7889-7893 [1993]).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise a cytotoxic agent, cytokine or growth inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active PRO molecules may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations of the PRO molecules may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and  $\gamma$ -ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT<sup>TM</sup> (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

#### N. Methods of Treatment

It is contemplated that the polypeptides, antibodies and other active compounds of the present invention may be used to treat various immune related diseases and conditions, such as T cell mediated diseases, including those characterized by infiltration of inflammatory cells into a tissue, stimulation of T-

cell proliferation, inhibition of T-cell proliferation, increased or decreased vascular permeability or the inhibition thereof.

Exemplary conditions or disorders to be treated with the polypeptides, antibodies and other compounds of the invention, include, but are not limited to systemic lupus erythematosus, rheumatoid arthritis, juvenile chronic arthritis, osteoarthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft-versus-host-disease.

In systemic lupus erythematosus, the central mediator of disease is the production of auto-reactive antibodies to self proteins/tissues and the subsequent generation of immune-mediated inflammation. Antibodies either directly or indirectly mediate tissue injury. Though T lymphocytes have not been shown to be directly involved in tissue damage, T lymphocytes are required for the development of auto-reactive antibodies. The genesis of the disease is thus T lymphocyte dependent. Multiple organs and systems are affected clinically including kidney, lung, musculoskeletal system, mucocutaneous, eye, central nervous system, cardiovascular system, gastrointestinal tract, bone marrow and blood.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that mainly involves the synovial membrane of multiple joints with resultant injury to the articular cartilage. The pathogenesis is T lymphocyte dependent and is associated with the production of rheumatoid factors, auto-antibodies directed against self IgG, with the resultant formation of immune complexes that attain high levels in joint fluid and blood. These complexes in the joint may induce the marked infiltrate of lymphocytes and monocytes into the synovium and subsequent marked synovial changes; the joint space/fluid is infiltrated by similar cells with the addition of numerous neutrophils. Tissues affected are primarily the joints, often in symmetrical pattern. However, extra-articular disease also occurs in two major forms. One form is the development of extra-articular lesions with ongoing progressive joint disease and typical lesions of pulmonary fibrosis, vasculitis, and cutaneous ulcers. The second form of extra-articular disease is the so called Felty's syndrome which occurs late in the RA disease course, sometimes after joint disease has become quiescent, and involves the presence of neutropenia, thrombocytopenia and splenomegaly. This can be accompanied by vasculitis in multiple organs with formations of infarcts, skin

ulcers and gangrene. Patients often also develop rheumatoid nodules in the subcutis tissue overlying affected joints; the nodules late stage have necrotic centers surrounded by a mixed inflammatory cell infiltrate. Other manifestations which can occur in RA include: pericarditis, pleuritis, coronary arteritis, interstitial pneumonitis with pulmonary fibrosis, keratoconjunctivitis sicca, and rheumatoid nodules.

5 Juvenile chronic arthritis is a chronic idiopathic inflammatory disease which begins often at less than 16 years of age. Its phenotype has some similarities to RA; some patients which are rheumatoid factor positive are classified as juvenile rheumatoid arthritis. The disease is sub-classified into three major categories: pauciarticular, polyarticular, and systemic. The arthritis can be severe and is typically destructive and leads to joint ankylosis and retarded growth. Other manifestations can include chronic  
10 anterior uveitis and systemic amyloidosis.

Spondyloarthropathies are a group of disorders with some common clinical features and the common association with the expression of HLA-B27 gene product. The disorders include: ankylosing spondylitis, Reiter's syndrome (reactive arthritis), arthritis associated with inflammatory bowel disease, spondylitis associated with psoriasis, juvenile onset spondyloarthropathy and undifferentiated  
15 spondyloarthropathy. Distinguishing features include sacroileitis with or without spondylitis; inflammatory asymmetric arthritis; association with HLA-B27 (a serologically defined allele of the HLA-B locus of class I MHC); ocular inflammation, and absence of autoantibodies associated with other rheumatoid disease. The cell most implicated as key to induction of the disease is the CD8+ T lymphocyte, a cell which targets antigen presented by class I MHC molecules. CD8+ T cells may react against the class I MHC allele HLA-  
20 B27 as if it were a foreign peptide expressed by MHC class I molecules. It has been hypothesized that an epitope of HLA-B27 may mimic a bacterial or other microbial antigenic epitope and thus induce a CD8+ T cells response.

Systemic sclerosis (scleroderma) has an unknown etiology. A hallmark of the disease is induration of the skin; likely this is induced by an active inflammatory process. Scleroderma can be localized or  
25 systemic; vascular lesions are common and endothelial cell injury in the microvasculature is an early and important event in the development of systemic sclerosis; the vascular injury may be immune mediated. An immunologic basis is implied by the presence of mononuclear cell infiltrates in the cutaneous lesions and the presence of anti-nuclear antibodies in many patients. ICAM-1 is often upregulated on the cell surface of fibroblasts in skin lesions suggesting that T cell interaction with these cells may have a role in the  
30 pathogenesis of the disease. Other organs involved include: the gastrointestinal tract: smooth muscle atrophy and fibrosis resulting in abnormal peristalsis/motility; kidney: concentric subendothelial intimal proliferation affecting small arcuate and interlobular arteries with resultant reduced renal cortical blood flow, results in proteinuria, azotemia and hypertension; skeletal muscle: atrophy, interstitial fibrosis; inflammation; lung: interstitial pneumonitis and interstitial fibrosis; and heart: contraction band necrosis,  
35 scarring/fibrosis.

Idiopathic inflammatory myopathies including dermatomyositis, polymyositis and others are disorders of chronic muscle inflammation of unknown etiology resulting in muscle weakness. Muscle injury/inflammation is often symmetric and progressive. Autoantibodies are associated with most forms. These myositis-specific autoantibodies are directed against and inhibit the function of components, proteins  
40 and RNA's, involved in protein synthesis.

Sjögren's syndrome is due to immune-mediated inflammation and subsequent functional destruction of the tear glands and salivary glands. The disease can be associated with or accompanied by inflammatory connective tissue diseases. The disease is associated with autoantibody production against Ro and La antigens, both of which are small RNA-protein complexes. Lesions result in keratoconjunctivitis sicca, xerostomia, with other manifestations or associations including biliary cirrhosis, peripheral or sensory neuropathy, and palpable purpura.

Systemic vasculitis are diseases in which the primary lesion is inflammation and subsequent damage to blood vessels which results in ischemia/necrosis/degeneration to tissues supplied by the affected vessels and eventual end-organ dysfunction in some cases. Vasculitides can also occur as a secondary lesion or sequelae to other immune-inflammatory mediated diseases such as rheumatoid arthritis, systemic sclerosis, *etc.*, particularly in diseases also associated with the formation of immune complexes. Diseases in the primary systemic vasculitis group include: systemic necrotizing vasculitis: polyarteritis nodosa, allergic angiitis and granulomatosis, polyangiitis; Wegener's granulomatosis; lymphomatoid granulomatosis; and giant cell arteritis. Miscellaneous vasculitides include: mucocutaneous lymph node syndrome (MLNS or Kawasaki's disease), isolated CNS vasculitis, Behet's disease, thromboangiitis obliterans (Buerger's disease) and cutaneous necrotizing venulitis. The pathogenic mechanism of most of the types of vasculitis listed is believed to be primarily due to the deposition of immunoglobulin complexes in the vessel wall and subsequent induction of an inflammatory response either via ADCC, complement activation, or both.

Sarcoidosis is a condition of unknown etiology which is characterized by the presence of epithelioid granulomas in nearly any tissue in the body; involvement of the lung is most common. The pathogenesis involves the persistence of activated macrophages and lymphoid cells at sites of the disease with subsequent chronic sequelae resultant from the release of locally and systemically active products released by these cell types.

Autoimmune hemolytic anemia including autoimmune hemolytic anemia, immune pancytopenia, and paroxysmal nocturnal hemoglobinuria is a result of production of antibodies that react with antigens expressed on the surface of red blood cells (and in some cases other blood cells including platelets as well) and is a reflection of the removal of those antibody coated cells via complement mediated lysis and/or ADCC/Fc-receptor-mediated mechanisms.

In autoimmune thrombocytopenia including thrombocytopenic purpura, and immune-mediated thrombocytopenia in other clinical settings, platelet destruction/removal occurs as a result of either antibody or complement attaching to platelets and subsequent removal by complement lysis, ADCC or FC-receptor mediated mechanisms.

Thyroiditis including Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, and atrophic thyroiditis, are the result of an autoimmune response against thyroid antigens with production of antibodies that react with proteins present in and often specific for the thyroid gland. Experimental models exist including spontaneous models: rats (BUF and BB rats) and chickens (obese chicken strain); inducible models: immunization of animals with either thyroglobulin, thyroid microsomal antigen (thyroid peroxidase).

Type I diabetes mellitus or insulin-dependent diabetes is the autoimmune destruction of pancreatic islet  $\beta$  cells; this destruction is mediated by auto-antibodies and auto-reactive T cells. Antibodies to insulin or the insulin receptor can also produce the phenotype of insulin-non-responsiveness.

Immune mediated renal diseases, including glomerulonephritis and tubulointerstitial nephritis, are the result of antibody or T lymphocyte mediated injury to renal tissue either directly as a result of the production of autoreactive antibodies or T cells against renal antigens or indirectly as a result of the deposition of antibodies and/or immune complexes in the kidney that are reactive against other, non-renal antigens. Thus other immune-mediated diseases that result in the formation of immune-complexes can also induce immune mediated renal disease as an indirect sequelae. Both direct and indirect immune mechanisms result in inflammatory response that produces/induces lesion development in renal tissues with resultant organ function impairment and in some cases progression to renal failure. Both humoral and cellular immune mechanisms can be involved in the pathogenesis of lesions.

Demyelinating diseases of the central and peripheral nervous systems, including Multiple Sclerosis; idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome; and Chronic Inflammatory Demyelinating Polyneuropathy, are believed to have an autoimmune basis and result in nerve demyelination as a result of damage caused to oligodendrocytes or to myelin directly. In MS there is evidence to suggest that disease induction and progression is dependent on T lymphocytes. Multiple Sclerosis is a demyelinating disease that is T lymphocyte-dependent and has either a relapsing-remitting course or a chronic progressive course. The etiology is unknown; however, viral infections, genetic predisposition, environment, and autoimmunity all contribute. Lesions contain infiltrates of predominantly T lymphocyte mediated, microglial cells and infiltrating macrophages; CD4+ T lymphocytes are the predominant cell type at lesions. The mechanism of oligodendrocyte cell death and subsequent demyelination is not known but is likely T lymphocyte driven.

Inflammatory and Fibrotic Lung Disease, including Eosinophilic Pneumonias; Idiopathic Pulmonary Fibrosis, and Hypersensitivity Pneumonitis may involve a dysregulated immune-inflammatory response. Inhibition of that response would be of therapeutic benefit.

Autoimmune or Immune-mediated Skin Disease including Bullous Skin Diseases, Erythema Multiforme, and Contact Dermatitis are mediated by auto-antibodies, the genesis of which is T lymphocyte-dependent.

Psoriasis is a T lymphocyte-mediated inflammatory disease. Lesions contain infiltrates of T lymphocytes, macrophages and antigen processing cells, and some neutrophils.

Allergic diseases, including asthma; allergic rhinitis; atopic dermatitis; food hypersensitivity; and urticaria are T lymphocyte dependent. These diseases are predominantly mediated by T lymphocyte induced inflammation, IgE mediated-inflammation or a combination of both.

Transplantation associated diseases, including Graft rejection and Graft-Versus-Host-Disease (GVHD) are T lymphocyte-dependent; inhibition of T lymphocyte function is ameliorative.

Other diseases in which intervention of the immune and/or inflammatory response have benefit are infectious disease including but not limited to viral infection (including but not limited to AIDS, hepatitis A, B, C, D, E and herpes) bacterial infection, fungal infections, and protozoal and parasitic infections (molecules (or derivatives/agonists) which stimulate the MLR can be utilized therapeutically to enhance the

immune response to infectious agents), diseases of immunodeficiency (molecules/derivatives/agonists) which stimulate the MLR can be utilized therapeutically to enhance the immune response for conditions of inherited, acquired, infectious induced (as in HIV infection), or iatrogenic (*i.e.*, as from chemotherapy) immunodeficiency, and neoplasia.

5 It has been demonstrated that some human cancer patients develop an antibody and/or T lymphocyte response to antigens on neoplastic cells. It has also been shown in animal models of neoplasia that enhancement of the immune response can result in rejection or regression of that particular neoplasm. Molecules that enhance the T lymphocyte response in the MLR have utility *in vivo* in enhancing the immune response against neoplasia. Molecules which enhance the T lymphocyte proliferative response in the MLR  
10 (or small molecule agonists or antibodies that affected the same receptor in an agonistic fashion) can be used therapeutically to treat cancer. Molecules that inhibit the lymphocyte response in the MLR also function *in vivo* during neoplasia to suppress the immune response to a neoplasm; such molecules can either be expressed by the neoplastic cells themselves or their expression can be induced by the neoplasm in other cells. Antagonism of such inhibitory molecules (either with antibody, small molecule antagonists or other  
15 means) enhances immune-mediated tumor rejection.

Additionally, inhibition of molecules with proinflammatory properties may have therapeutic benefit in reperfusion injury; stroke; myocardial infarction; atherosclerosis; acute lung injury; hemorrhagic shock; burn; sepsis/septic shock; acute tubular necrosis; endometriosis; degenerative joint disease and pancreatitis.

The compounds of the present invention, *e.g.*, polypeptides or antibodies, are administered to a  
20 mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation (intranasal, intrapulmonary) routes. Intravenous or inhaled administration of polypeptides and antibodies is preferred.

In immunoadjuvant therapy, other therapeutic regimens, such administration of an anti-cancer  
25 agent, may be combined with the administration of the proteins, antibodies or compounds of the instant invention. For example, the patient to be treated with a the immunoadjuvant of the invention may also receive an anti-cancer agent (chemotherapeutic agent) or radiation therapy. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy  
30 are also described in *Chemotherapy Service* Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992). The chemotherapeutic agent may precede, or follow administration of the immunoadjuvant or may be given simultaneously therewith. Additionally, an anti-estrogen compound such as tamoxifen or an anti-progesterone such as onapristone (see, EP 616812) may be given in dosages known for such molecules.

It may be desirable to also administer antibodies against other immune disease associated or tumor  
35 associated antigens, such as antibodies which bind to CD20, CD11a, CD18, ErbB2, EGFR, ErbB3, ErbB4, or vascular endothelial factor (VEGF). Alternatively, or in addition, two or more antibodies binding the same or two or more different antigens disclosed herein may be coadministered to the patient. Sometimes, it may be beneficial to also administer one or more cytokines to the patient. In one embodiment, the PRO polypeptides are coadministered with a growth inhibitory agent. For example, the growth inhibitory agent  
40 may be administered first, followed by a PRO polypeptide. However, simultaneous administration or

administration first is also contemplated. Suitable dosages for the growth inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth inhibitory agent and the PRO polypeptide.

For the treatment or reduction in the severity of immune related disease, the appropriate dosage of an a compound of the invention will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the agent is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the compound, and the discretion of the attending physician. The compound is suitably administered to the patient at one time or over a series of treatments.

For example, depending on the type and severity of the disease, about 1 µg/kg to 15 mg/kg (*e.g.*, 0.1-20 mg/kg) of polypeptide or antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

O. Articles of Manufacture

In another embodiment of the invention, an article of manufacture containing materials (*e.g.*, comprising a PRO molecule) useful for the diagnosis or treatment of the disorders described above is provided. The article of manufacture comprises a container and an instruction. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for diagnosing or treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is usually a polypeptide or an antibody of the invention. An instruction or label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

P. Diagnosis and Prognosis of Immune Related Disease

Cell surface proteins, such as proteins which are overexpressed in certain immune related diseases, are excellent targets for drug candidates or disease treatment. The same proteins along with secreted proteins encoded by the genes amplified in immune related disease states find additional use in the diagnosis and prognosis of these diseases. For example, antibodies directed against the protein products of genes amplified in multiple sclerosis, rheumatoid arthritis, or another immune related disease, can be used as diagnostics or prognostics.

For example, antibodies, including antibody fragments, can be used to qualitatively or quantitatively detect the expression of proteins encoded by amplified or overexpressed genes ("marker gene products"). The antibody preferably is equipped with a detectable, *e.g.*, fluorescent label, and binding can be

monitored by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. These techniques are particularly suitable, if the overexpressed gene encodes a cell surface protein. Such binding assays are performed essentially as described above.

*In situ* detection of antibody binding to the marker gene products can be performed, for example, by immunofluorescence or immunoelectron microscopy. For this purpose, a histological specimen is removed from the patient, and a labeled antibody is applied to it, preferably by overlaying the antibody on a biological sample. This procedure also allows for determining the distribution of the marker gene product in the tissue examined. It will be apparent for those skilled in the art that a wide variety of histological methods are readily available for *in situ* detection.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

#### EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

#### EXAMPLE 1: Microarray analysis of stimulated T-cells

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (in this instance, activated CD4+ T cells) sample is greater than hybridization signal of a probe from a control (in this instance, non-stimulated CD4 + T cells) sample, the gene or genes overexpressed in the test tissue are identified. The implication of this result is that an overexpressed protein in a test tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In one example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in PCT Patent Application Serial No. PCT/US01/10482, filed on March 30, 2001 and which is herein incorporated by reference.

In this experiment, CD4+ T cells were purified from a single donor using the RosetteSep™ protocol from (Stem Cell Technologies, Vancouver BC) which contains anti-CD8, anti-CD16, anti-CD19, anti-CD36 and anti-CD56 antibodies used to produce a population of isolated CD4 + T cells. Isolated CD4+

T cells were activated with an anti-CD3 antibody (used at a concentration that does not stimulate proliferation) together with either ICAM-1 or anti-CD28 antibody. At 24 or 72 hours cells were harvested, RNA extracted and analysis run on Affimax (Affymetrix Inc. Santa Clara, CA) microarray chips. Non-stimulated (resting) cells were harvested immediately after purification, and subjected to the same analysis.

- 5 Genes were compared whose expression was upregulated at either of the two timepoints in activated vs. resting cells.

Below are the results of these experiments, demonstrating that various PRO polypeptides of the present invention are differentially expressed in isolated CD4 + T cells activated by anti-CD3/ICAM-1 or anti-CD3/anti-CD28 as compared to isolated resting CD4+ T cells. As described above, these data  
10 demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more immune disorders, but also serve as therapeutic targets for the treatment of those immune disorders.

The results of this experiment are Figures 1-7589 show increase or decrease in expression upon stimulation with anti-CD3/ICAM1 and also show increase or decrease in expression upon stimulation with  
15 anti-CD3/anti-CD28. The nucleic acids and encoded proteins of Figure 946, Figure 1520, Figure 1574, Figure 1622, Figure 1816, Figure 2433, Figure 2986, Figure 3220, Figure 4120 and Figure 5421 are significantly overexpressed in isolated CD4 + T cells activated by anti-CD3/ICAM-1 or anti-CD3/anti-CD28 as compared to isolated resting CD4+ T cells.

20 EXAMPLE 2: Use of PRO as a hybridization probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in  
25 human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing  
30 of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

EXAMPLE 3: Expression of PRO in *E. coli*

35 This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is  
40 pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and

tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.71 g sodium citrate•2H<sub>2</sub>O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO<sub>4</sub>) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

*E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### EXAMPLE 4: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., *Cell*, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl<sub>2</sub>. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO<sub>4</sub>, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml <sup>35</sup>S-cysteine and 200 µCi/ml <sup>35</sup>S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter,

and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompayrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO<sub>4</sub> or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as <sup>35</sup>S-methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 promoter/enhancer containing vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 promoter/enhancer containing vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni<sup>2+</sup>-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Quiagen), Dosper® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas et al., *supra*. Approximately  $3 \times 10^7$  cells are frozen in an ampule for further growth and production as described below.

5 The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mL of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2  $\mu$ m filtered PS20 with 5% 0.2  $\mu$ m diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a  
10 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with  $3 \times 10^5$  cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at  $1.2 \times 10^6$  cells/mL. On day 0, pH is determined. On  
15 day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22  $\mu$ m filter.  
20 The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column  
25 is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The  
30 conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275  $\mu$ l of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The  
35 homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### EXAMPLE 5: Expression of PRO in Yeast

40 The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### EXAMPLE 6: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (PharMingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni<sup>2+</sup>-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl<sub>2</sub>; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni<sup>2+</sup>-NTA agarose column (commercially available from Qiagen) is prepared

with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline  $A_{280}$  with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching  $A_{280}$  baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with  $Ni^{2+}$ -NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His<sub>10</sub>-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### EXAMPLE 7: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion

chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

#### EXAMPLE 8: Purification of PRO Polypeptides Using Specific Antibodies

5 Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

10 Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB  
15 Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the  
20 addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high  
25 ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

#### EXAMPLE 9: Drug Screening

30 This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment.  
35 Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

#### EXAMPLE 10: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of a PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which

subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.